A STUDY ON SIGNIFICANCE OF FIBRINOGEN AS A RISK FACTOR FOR ISCHEMIC STROKE AND ITS CORRELATION WITH SEVERITY AND FUNCTIONAL OUTCOME OF ISCHEMIC STROKE

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON SIGNIFICANCE OF FIBRINOGEN AS A RISK FACTOR FOR ISCHEMIC STROKE AND ITS CORRELATION WITH SEVERITY AND FUNCTIONAL OUTCOME OF ISCHEMIC STROKE"** submitted by **Dr.K.NACHIAPPAN** to The Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfillment of the requirement for the award of M.D. degree Branch I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I **Dr. K.NACHIAPPAN** declare that I carried out this work on **"A STUDY ON SIGNIFICANCE OF FIBRINOGEN AS A RISK FACTOR FOR ISCHEMIC STROKE AND ITS CORRELATION WITH SEVERITY AND FUNCTIONAL OUTCOME OF ISCHEMIC STROKE"** at Department of General Medicine, Government Rajaji Hospital during the period of April 2012 – October 2012. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, and diploma to any university, board either in India or abroad.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M.D. Degree examination in General Medicine.

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CONTENTS

INTRODUCTION

Strokes are the most important cause of prolonged disability. About 15% to 25% of stroke survivors become disabled permanently, while 20%remain in institutional care for three months after their stroke. The psychological and economical burdens of stroke are enormous. Stroke is one of the major illnesses in all over the world. Stroke is the most common cause of death after cardiac disease and cancer. It plays an important role in the morbidity and mortality in the elderly and late middle age persons. Cerebrovascular disease stands first in frequency among the neurologic diseases.

Because of the raising in the number of aging population, the burden of stroke is likely to increase automatically in the near future. Early identification of risk factors associated with stroke and implementing prevention programs will definitely help to control the burden of this major epidemic. Stroke is a heterogeneous disease. Ischemic and hemorrhagic strokes are the two major types of stroke with different pathogenesis and outcome.

Various studies demonstrate an association between fibrinogen levels and ischemic stroke prognosis. Every study shows a worse in prognosis in ischemic stroke patients with high fibrinogen level at the time of stroke.

This study attempts to identify the significance of plasma fibrinogen as a risk factor as well as prognostic factor for ischemic stroke patients and also to study the correlation between the plasma fibrinogen levels and other major risk factors for ischemic stroke.

The primary goal of biomarker plasma fibrinogen in ischemic stroke patients is early identification of high risk individuals who can be targeted for aggressive acute management and improved secondary prevention measures. Many secondary prevention interventions[62] in particular diet, exercise, smoking cessation and drugs [fibrates, omega 3 fatty acids, ticlopidine and pentoxifylline][61] all reduce fibrinogen levels and minimize vascular risk.

AIM OF THE STUDY

To study the significance of plasma fibrinogen in ischemic stroke patients as a risk factor.

To study the correlation of plasma fibrinogen in ischemic stroke with special reference to risk factors such as age, sex, smoking, alcoholism, hypertension, diabetes mellitus and obesity.

To study the correlation between initial fibrinogen levels and functional outcome and severity of ischemic stroke.

REVIEW OF LITERATURE

Cerebrovascular disease most commonly presents as an acute focal stroke. Stroke is a clinical syndrome characterized by acute loss of focal brain function or monocular function with symptoms lasting more than 24 hours. It is due to inadequate cerebral or ocular blood supply. The clinical symptoms of stroke are highly variable because of the complex anatomy of the brain and its vasculature. About 85% of all stroke are ischemic 10% are due to intra cerebral hemorrhage and 5% are due to subarachnoid hemorrhage in the community. Ischemic arterial disease may present, particularly in elderly with a gradual decline in intellectual function with motor weakness or with or without sensory weakness or gait disorder. Hemorrhagic stroke occurs mostly due to rupture of the major cerebral arteries of the circle of Willis in to the subarachnoid space.

Cerebral ischemia is caused by a prolonged reduction in blood supply that lasts longer than several seconds. Neurological symptoms manifest within seconds when the neurons are devoid of glycogen and ATP.

The normal cerebral blood flow (CBF) in man is 50ml/100gms of brain/min. Using Positron Emission Tomography, the cerebral energy metabolism is evaluated by cerebral metabolic rate of oxygen (CMRO2) and of glucose (CMR glu). It has also been found that the oxygen extraction fraction (OEF) remains constant throughout the brain. So in resting normal brain, the CBF is a reliable reflection of CMRO2.

In ischemia when CBF reduces below about 20ml/100g/min, the oxygen extraction fraction becomes higher and the CMRO2 begins to reduce. Infact a high OEF is only seen nearly after acute ischemic stroke, in the first day or so. If the blood supply is restored, functional recovery is still possible. If blood flow is quickly restored brain tissue can recover fully and patient's symptoms are only transient; it is defined as transient ischemic attack [TIA].

Typically the neurologic signs and symptoms of a TIA last for 5 to 15 minutes. But by definition symptoms should recover within less than 24 hours. Stroke will occur when the signs and symptoms last for more than 24hours. Focal ischemia or infarction is usually caused by thrombosis of the cerebral vessels or by emboli from proximal arteries or heart.

In ischemia, due to ineffective anaerobic metabolism of glucose, lactate synthesis increases and the pH falls. ATP synthesis is impaired. As the cerebral blood flow reduces further, energy-dependent functions of the cell membranes become increasingly damaged. Water, Sodium, calcium and Chloride enter the cells and Potassium (K+) leaks out. Potentially neurotoxic transmitters such as L-glutamate, oxygen radicals and lipid peroxides are formed and will damage the cells further.

Fall in cerebral blood flow to zero cause infarction within 4 to 10min. When cerebral blood flow less than 16 to 18ml/100g tissue per min cause infarction within 60 minutes. When the blood supply becomes further less than 10ml/100gm/min, infarction occurs and if blood flow is restored,

neurological function does not come back. At this point, the CMRO2 and CMF will be low and OEF will be normal indicating metabolic depression.

Sometimes oxygen extraction fraction is low and the cerebral blood flow is in excess of requirements for the low metabolic demands of the infarcted tissue. It is known as luxury perfusion. In absolute luxury perfusion, CBF is increased which is termed as hyper perfusion.

Factors determining the metabolic consequences.

1. Duration of ischemia
2. Collateral blood supply
3. Development of cerebral edema
4. Raised intracranial pressure
5. Vasoconstrictor prostaglandins released from aggregating platelets and
6. Blood viscosity and aggregation of formed elements slow the microcirculation and promote thrombosis
7. Hyperglycemia of stress response reflect the severity of initial stroke
8. Systemic hypoxia (as a consequence of pneumonia etc.) and
9. Dehydration by, increasing the hematocrit and blood viscosity.
10. Free radical damage.

Free Radical Damage

Three major molecular events in brain damage from cerebrovascular occlusion are

1. Calcium overload,

2. Excessive acidosis, and
3. Enhanced production of free radicals.

Free radicals are produced in increased amounts under ischemic conditions and damage proteins, nucleic acids, and membrane lipids, disrupting cellular integrity. This oxygen radical activity is especially very intense during reperfusion after sustained ischemia. The generation of hydroxyl radical, the most toxic and reactive of free radicals, is catalyzed by ferrous iron released from intra cellular stores during ischemia. Brain cells release glutamate as a result of stroke and glutamate initiates biochemical reactions that lead to brain cell death, including the production of free radicals.

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Cerebral hemorrhage produces neurologic symptoms by producing a mass effect on neural structures or from the toxic effects of blood itself.

BLOOD SUPPLY TO BRAIN

Anterior circulation - by means of one internal carotid artery each side. Each one supplies two fifths of total circulation of brain.

Posterior circulation - by means of two vertebral arteries which join to form basilar artery. It accounts for one fifth of total brain circulation.

It is important to note that the posterior circulation contains the brain stem, a midline important crucial structure.

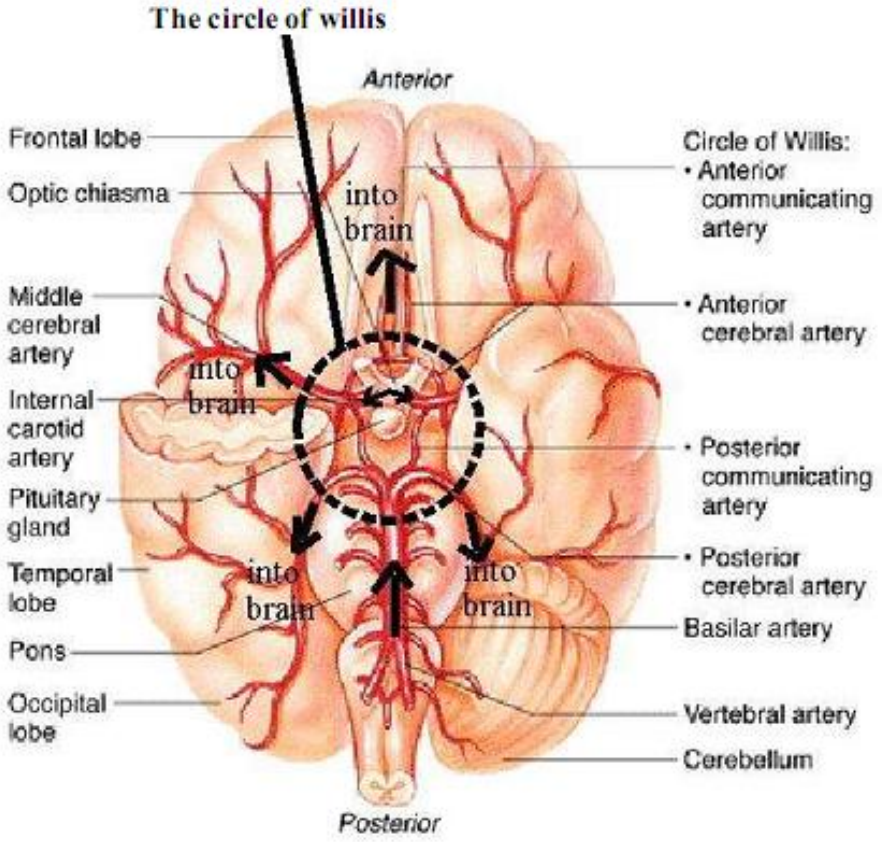
CIRCLE OF WILLIS:

Most important circle of Willis[1] lies in the inter peduncular fossa at the base of the brain. This circle is formed by anastomosis between the two internal carotid arteries and the two vertebral arteries. The anterior communicating artery, the anterior cerebral, internal carotid, posterior communicating, posterior cerebral and the basilar arteries all contribute to the circle. The circle of Willis allows blood that enters either by the internal carotid or by the vertebral arteries to be distributed to any part of either cerebral hemisphere. Circle of Willis also gives cortical and central branches that supply the brain.

CAROTID ARTERIAL SYSTEM:

The left common carotid artery originates directly from the aorta and right common carotid artery from the innominate artery. At the bifurcation of the common carotid artery, the internal carotid artery starts at the carotid sinus then it runs up the neck and reaches the base of the skull and reaches the carotid canal of the petrous bone. It then runs through the cavernous sinus, pierces the meninges and divides into anterior and middle cerebral arteries.

THE CIRCLE OF WILLIS



BRANCHES OF INTERNAL CAROTID ARTERY

OPHTHALMIC ARTERY:

The ophthalmic artery is the first main branch of the ICA. It arises in the cavernous sinus. It goes through the optic foramen to supply the eye and other structures in the orbit.

POSTERIOR COMMUNICATING ARTERY:

It is the next artery to branch from the internal carotid artery. It runs back to communicate the first part of the posterior cerebral artery, so contributing to the circle of Willis.

ANTERIOR CHOROIDAL ARTERY:

This develops from the last portion of the internal carotid artery and supplies optic tract, internal capsule, parts of basal ganglia, thalamus and optic radiation.

ANTERIOR CEREBRAL ARTERY:

The anterior cerebral artery goes to the inter-hemispheric fissure, joins with its counterpart of opposite anterior cerebral artery via anterior communicating artery, curves around the genu of corpus callosum and supplies the anterior and medial parts of the cerebral hemisphere.

MIDDLE CEREBRAL ARTERY

The middle cerebral artery goes to the sylvan fissure and gives branches which supply the lateral parts of the cerebral hemisphere. From its main trunk a medial and lateral group of tiny lenticulostriate arteries arise and

pass upwards to penetrate the base of the brain and the supply the basal ganglia and internal capsule. The artery gives blood supply to the whole of the motor cortex except the leg area.

VERTEBRO BASILAR SYSTEM:

VERTEBRAL ARTERY:

The vertebral artery, a branch of the proximal subclavian artery ascends to pass through the transverse foramina of the sixth to the second cervical vertebrae, giving off small muscular branches on its ascend up. It runs posteriorly around the atlas and enters the skull through the foramen magnum. It joins with the opposite vertebral artery on the vertebral surface of the brainstem to form the basilar artery. The vertebral artery gives branches to anterior and posterior spinal arteries, the posterior inferior cerebellar arteries and small penetrating branches to the medulla[2].

BASILAR ARTERY

The basilar artery runs ventral to the pons to the pontomidbrain junction in the inter peduncular cistern. It bifurcates there and gives two posterior cerebral arteries. Numerous small branches are given to the brain stem and cerebellum. It gives rise to the anterior inferior cerebellar artery and superior cerebellar artery.

POSTERIOR CEREBRAL ARTERY:

The posterior cerebral artery surrounds the midbrain close to the oculomotor nerve at the level of tentorium and gives blood supply to the

inferior part of the temporal lobe and the occipital lobe[3]. Many small branches supply the mid brain, thalamus, hypothalamus and geniculate bodies.

ARTERIES TO SPECIFIC BRAIN AREAS

Corpus striatum and internal capsule- medial and lateral striate central branch of the middle cerebral artery supply[4]; the central branches of the anterior cerebral artery supply the remainder of the structures.

Thalamus -The posterior cerebral, posterior communication and basilar arteries supply the thalamus.

Mid brain - The posterior cerebral, superior cerebellar and basilar arteries supply.

Pons - The basilar and anterior, inferior and superior cerebellar arteries supply the pons.

Medulla oblongata- The vertebral, anterior and posterior spinal, posterior inferior cerebellar and basilar arteries supply.

VEINS OF THE BRAIN

EXTERNAL CEREBRAL VEINS

Superior cerebral veins run upward over the lateral surface of the cerebral hemisphere and empty into the superior sagittal sinus. The **Superficial middle cerebral veins** empty the lateral surface of the cerebral hemisphere; it run inferiorly in the lateral sulcus and empty into the cavernous sinus. **Deep middle cerebral veins** the insula and is joined by the

anterior cerebral vein and striate veins to form the basilar vein. **Basilar vein** ultimately joins the great cerebral vein, which in turn drains into the straight sinus.

INTERNAL CEREBRAL VEINS:

There are two internal cerebral veins. Union of the thalamo striate vein and the choroidal vein at the interventricular foramen forms internal cerebral veins. These veins form the great cerebral vein that drains into the straight sinus.

EPIDEMIOLOGY

INCIDENCE OF STROKE:

Worldwide, stroke is the major disease. Ischemic stroke is the major determinant to disability, morbidity and mortality in the world[5]. The incidence of stroke rapidly rises with the age. About 25% incidence occurs below the age of 65 and 75% above the age of 65years.

In 1990 CVD cause 28% of the world's 50.4 million deaths and 9.7% of the 1.4 billion lost DALYs. In the year 2001, CVD was the cause for 29% of all deaths and 14 % of the 1.5 billion lost DALYs. By the year 2020, 32 % of all deaths will be due to CVD.

WHO estimates that CVD will cause totally 24.2million deaths by the year 2030 in the world. Of these,14.9 % of deaths in men and 13.1 % of deaths in women will be due to CHD. Stroke will be responsible for 10.4 % of all male deaths and 11.8 % of all female deaths.

The population based study was done by WHO collaborative study in Rohtak; in Haryana state [1971-74] showed an annual incidence of 33 per one lakh population per year.

Leeder compared the role of CVD in the death patterns of one low-income country(India) and four middle-income countries (Russia, Brazil, China, and South Africa) in 2000 and predicted that increase in the number of productive years lost due to CVD between 2000 and 2030 in India compared to other countries. South Africa, 28 %; China, 57 %; Brazil, 64 %; and India, 95%.

STROKE PREVALENCE:

Vellore study demonstrated that stroke prevalence rate per 1lakh population was 56.9 per 1,00,000 population. The prevalence in Indian Eastern part was 160-270 per 1, 00,000 population.

South Asians have a high prevalence of ischemic stroke, coronary heart disease, non-insulin-dependent diabetes, central obesity, insulin resistance, hypertension[6] and high stroke mortality. It seems to be due partly to genetic susceptibility of high lipoprotein(a) levels in south asians and also influenced by dietary and life style induced changes in lipid levels.

MORTALITY

WHO collaborative study described that both in developed and developing nations, nearly 33% of the stroke patients died within 3 weeks

and 48 percent expired within one year. Stroke is one of the topmost causes of death throughout the world.

RISK FACTORS FOR STROKE

AGE:

Age is one of the strongest risk factor for ischemic stroke, primary intra cerebral hemorrhage and subarachnoid hemorrhage[7]. It is one of the major factors which negatively influence the outcome of the stroke patients.

SEX:

Male sex is associated with increased risk of stroke and poor outcome.

RACE AND ETHNICITY

Studies showed no statistically significant difference among the stroke patients belonging to different races. Some study shows that there is generally a higher incidence of all stroke types and cerebral infarction in blacks[8].

Previous stroke

Recurrence rate of cerebral infarction is 10-30%. The first 6 months is the period of highest risk if the patient did not take any treatment[9].

MODIFIABLE RISK FACTORS

CIGARETTE SMOKING:

Cigarette smoking is a strongest risk factor for ischemic stroke and subarachnoid hemorrhage but there is less association with primary intra cerebral Hemorrhage. Smoking has been related to the extent of carotid disease in patients selected for angiography. Studies show that 50% increase

risk in stroke occurrences in smokers. Heavy smoking causes doubling of risk[10]. In the Framingham study, cessation of smoking eliminates the additional risk of stroke within 2 years of stopping.

ALCOHOL:

Heavy alcohol consumption is also an independent risk factor for ischemic stroke. Studies show an association between sudden heavy drinking and the onset of cerebral infarction in young adults[11]. Chronic light alcohol intake carries decreased risk of stroke.

Chronic heavy intake of alcohol 180 – 400 g/week is associated with an increased risk. But modest alcohol consumption may be protective for ischemic stroke.

BLOOD PRESSURE:

Hypertension aggravates the stroke risk by increasing the extent and severity of atheroma formation. Increasing blood pressure is strongly associated with increase in subsequent stroke risk with all the pathological types of small vessel disease with in the brain. Most studies considered the diastolic blood pressure most important risk factor. Prolonged treatment of diastolic BP to cause a decrease of 6 mm Hg decrease the stroke risk incidence by 40% and the benefits occur within 3 years[12]. The relationship with systolic blood pressure is found to be similar and possibly stronger, and even 'isolated' systolic hypertension is associated with increased risk [13]. Control of hypertension reduces the risk of stroke.

BLOOD LIPIDS:

The association between blood lipids and stroke is weaker than that for coronary artery disease, but studies have shown that increase in serum lipoprotein(a) associated with increase in incidence of stroke[14]. Framingham study shows a weak correlation between cholesterol and triglycerides and the risk of cerebral infarction.

DIABETES MELLITUS:

Diabetes mellitus can cause cerebrovascular atherosclerosis, cardiac embolism and rheological abnormalities and cause increase incidence of stroke. Diabetes mellitus increases the risk of cerebrovascular disease 2 to 4 fold compared with non-diabetic patients[15]. Diabetes mellitus increases mortality rate in ischemic stroke patients.

ATRIAL FIBRILLATION:

The most frequent cause of embolic stroke is atrial fibrillation. Atrial fibrillation causes it by virtue of clot forming in the left atrium. Both rheumatic and non-heumatic atrial fibrillation is associated with ischemic stroke. Atrial fibrillation causes 20% of all infarcts[16] and is associated with a relative risk of death from stroke. The risk of stroke is about 5% per year in non-rheumatic atrial fibrillation.

Myocardial infarction

Cerebral infarction takes place in between 1% and 1.25% of cases within 1 year after myocardial infarction[17]. A history of myocardial infarction is also considered as a risk factor for cerebral infarction.[18]

Other heart disease

Cardiac failure, coronary heart disease and angina increase the risk of cerebral infarction. While the hypertrophy of left ventricle quadruples the risk, independent of hypertension.[19]

EXERCISE

Lack of physical activity is correlated with increased risk of ischemic stroke[20].

INFECTIONS AND INFLAMMATIONS:

There is evidence of an association between stroke and serum CRP[20] [C reactive protein]. High sensitive CRP [Hs CRP] elevated in case of inflammations and infections. High initial Hs CRP makes prognosis worse. The acute-phase reactant, CRP, a simple marker of inflammation, has now viewed as a major cardiovascular risk factor. CRP is composed of five 23-kDa subunits. CRP mainly produced primarily from the liver. Studies have found that cells within human arteries, particularly in the atherosclerotic intima, can also synthesis CRP. Studies have demonstrated that CRP, when measured with high-sensitivity assays [Hs CRP] strongly and independently predicts risk of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. Most significantly, hsCRP predicts prognosis at all levels of LDL cholesterol and at all levels of risk and at all age group as determined by the Framingham risk score.

Other markers of inflammation have predicted vascular risk.

These include

1, Interleukin-6,

2, Intercellular adhesion molecule (sICAM-1), soluble forms of certain cell adhesion molecules,

3, P-selectin, or the mediator CD40 ligand, as well as

4, Myeloperoxidase- markers of leukocyte activation,

5, Lipoprotein-associated phospholipase A2 and pregnancy-associated plasma proteinA - inflammatory markers associated with lipid oxidation.

Some of these markers have very short half-life for use in clinical diagnostic testing, whereas the others predict risk in large populations very marginally with high cost. So, continued evaluation of other inflammatory biomarkers may be the next big targets for identification and monitoring of therapy, particularly in the case of acute ischemic stroke.

Hyperhomocysteinemia.

Studies showed that hyperhomocysteinemia related to ischemic stroke and coronary artery disease[21]. Homocysteine is an amino acid having sulfhydryl group. It is derived from the demethylation of dietary methionine. Patients with rare inherited deficiency of methionine metabolism will develop severe hyperhomocysteinemia. Plasma levels of homocysteine will be higher than 100μmol/liter [normal up to 15 μmol/ liter].They have significantly elevated risk of premature atherothrombosis as well as venous thrombosis.

Mechanisms responsible for these effects include endothelial dysfunction, accelerated LDL cholesterol oxidation, impairment of flow-mediated endothelium-derived relaxing factor with subsequent reduction in arterial vasodilatation, activation of platelets and their aggregation and oxidative stress. Mild to moderate hyperhomocysteinemia (plasma levels more than 15μmol/liter) are more common primarily because of reduced dietary intake of folic acid. Heterozygotes for cystathionine synthetase deficiency have moderately raised levels of blood homocysteine.

TRANSIENT ISCHEMIC ATTACKS:

TIA [transient ischemic attack] has five to ten fold excess risk of ischemic stroke. About 15% of first ischemic stroke patients have had earlier TIAs, but only about 50% of them get consultation. So, the incidence of TIAs seeking medical care is an underestimate of the real problems.

By definition, TIA has symptoms lasting for less than 24 hours, but few patients have some residual neurological signs of no functional significance and no symptoms. About 30% patients will have focal hypo density lesion on CT brain. Even higher percentage of patients has focal lesions on MRI.

The main aim of CT and MRI brain imaging is to find out any structural lesion causing 'transient focal neurological attacks'.

Causes of transient focal neurological attacks

1. TIA – cerebral ischemia
2. Migraine with aura
3. Partial epileptic seizures
4. Space occupying intracranial lesions – tumour, hematoma etc
5. vascular malformation, Giant aneurysm
6. Multiple sclerosis
7. Labyrinthine disorders
8. Metabolic – hypoglycemia, hyperglycemia and electrolyte abnormalities
9. Psychological

CARDIOVASCULAR DISEASES:

ECG abnormalities showing hypertension and coronary artery disease are risk factors for ischemic stroke. History of angina or myocardial infarction is highly associated with stroke incidence. Rheumatic heart disease and cardiac failure are other cardiac risk factors. Claudication is an additional risk factor for both stroke and myocardial infarction. Claudication reflects atheromatous disease in peripheral circulation.

CAROTID ARTERY DISEASE:

When carotid artery stenosis is greater than three fourths of the circumference, combined transient ischemic attack[22] and stroke incidence rate is 10.5% per year.

PLASMA FIBRINOGEN:

Fibrinogen itself is a strong independent risk factor for coronary artery disease and stroke. Plasma fibrinogen plays a role in platelet aggregation and contributes to blood viscosity, combines with thrombin and mediates the final step in clot formation.

Fibrinogen has been positively associated with age, obesity, smoking, diabetes, and LDL cholesterol level. It was associated inversely with HDL cholesterol level, alcohol and exercise level. Fibrinogen like CRP, is an acute-phase reactant and increases during inflammation.

Reports from various studies such as Gothenburg, Northwick Park, and Framingham heart studies all found significant positive associations between fibrinogen and future risk of cardiovascular events[23].In one study, the age and gender adjusted hazard ratio per 1g/liter rise in plasma fibrinogen was 2.4 for coronary heart disease and 2.1 for stroke.

Qizibash N et al [35] identified in two prospective observational studies the importance of fibrinogen for prediction of ischemic stroke independent of other haemostatic factors such as Von Willebrand factor, tissue plasminogen activator and packed cell volume.

Fibrinogen should be included in the assessment of individual risk factors for ischemic stroke. Fibrinogen is the most significant potentially treatable risk factor for ischemic stroke. There are several mechanisms by which fibrinogen can promote thrombosis through hypercoaguable state, the

acceleration of atherosclerosis or by reduction of blood flow by reducing vascular relaxation factor and or due to high blood or plasma viscosity. However high blood viscosity per se, has not consistently been found to be a risk factor for stroke.

In recent meta-analytic study, there was a significant linear logarithmic association between fibrinogen level and the risk of coronary heart disease and ischemic stroke. More studies showed that the prediction of risk of ischemic stroke will be high when both hsCRP and fibrinogen levels are utilized.

OTHER RISK FACTORS:

Abdominal obesity, left ventricular hypertrophy, diagonal ear lobe crease, corneal arcus and snoring are other risk factors.

CLASSIFICATION OF STROKE [2, 24]

Stroke can be classified in several ways

PATHOPHYSIOLOGICAL CLASSIFICATION

Ischemic

TOAST trial of org acute stroke treatment – classified as

A) Thrombotic

- Small vessel occlusion – [SVO]
- Large artery atherosclerosis - [LAA]

B) Embolic

- Cardio embolic occlusion - [CEO]

- Artery – artery embolic

- Unclassified

- Hematologic

- Others

II Hemorrhagic

i) Intra parenchymal

ii) Subarachnoid

B) **Anatomic classification:**

I. by Vascular supply

a. Carotid

b. Vertebro basilar

II. By location

a. supra tentorial

- Lobar

- Ganglionic/thalamic

b. Infratentorial

- Cerebellar

PATHOLOGY

There are two major types of brain damage in stroke patients,

1. ISCHEMIA: A lack of blood supply depriving brain tissue of needed fuel and oxygen.

2. HEMORRHAGE: The release of blood into brain and extra vascular space within the cranium, which in turn damages the brain by causing localized or generalized injury.

Cerebral ischemia can cause brain damage temporarily and permanently. Permanent damage cause cerebral infarction.

It can be divided into a) thrombosis b) embolism and c) decreased systemic perfusion.

Thrombosis: The most common pathology is atherosclerosis. They can block large arteries and penetrating arteries. Other common pathologies are arteritis (takayasu, giant cell etc.), fibro muscular dysplasia, dissection of vessel wall, and hemorrhage into plaque.

Embolism: Emboli formed elsewhere within the vascular system goes to distal vessel and blocks the blood flow. These arise proximally, more commonly from the heart, or from major arteries such as aorta, carotid, vertebral arteries and from systemic veins.

Cardiac sources include from heart valves, endocardial surface and clot or tumors.

Decreased systemic perfusion: Most commonly due to systemic hypotension, hypovolemia or cardiac pump failure. Poor perfusion will result in watershed zone infarct.

Pathophysiology of acute cerebral ischemia

Atherosclerosis

Atherosclerosis is a primary process responsible for vessel occlusion. It affects primarily elastic arteries [aorta, carotid, iliac arteries etc.]. Various studies described atherosclerosis not a simple disease of lipid deposition rather systemic inflammation plays a role in atherosclerotic plaque. Studies demonstrate heavy infiltration of inflammatory cells at the site of plaque rupture**.**

When cerebral blood flow falls and the brain become ischemic, a series of pathophysiological and functional changes occur before cell death. Cerebral ischemia causes not only reversible but also irreversible loss of brain function, when neurons are devoid of glucose and ATP. It also causes cerebral edema [Ischemic edema]. Cerebral edema is partly cytotoxic and partly vasogenic. Ischemic cerebral edema is maximum in 2-4 days and subsides within a week.

Cytotoxic edema starts within minutes of stroke onset. It affects the grey matter more than the white matter. It is because of damaged cell membrane that allows intracellular water to accumulate.

Vasogenic edema starts later, within hours of stroke onset. It affects the white matter more than the grey matter. It is due to the damaged blood-brain barrier which allows plasma constituents to enter the extracellular space.

DIAGNOSIS

The diagnosis of stroke is easy if there is any history of sudden onset of focal neurological dysfunction usually first noticed on getting up from the bed in the early morning. Patient will be over the age of 50 years and also has vascular risk factors.

Progression of symptoms occur over the first few minutes or hours, but usually the deficit become stabilized by 12-24 hours and, the recovery starts within a few days in many cases. The severity ranges from a minimal deficit, which disappears in a day, through a persistent deficit with or without disability, to death.

If the history is clear, CT or MRI brain scan will show an infarct or hemorrhage. Brain imaging is normal in the case of early infarction or very small lesion. If there is any doubt about the speed of onset of a focal neurological deficit, the diagnosis is most likely to be an intracranial space occupying lesion, such as a tumor or chronic subdural hematoma. Intracranial tumor will have recent headache, seizures, papilledema and worsening of neurological deficit over long time.

Chronic subdural hematoma patients will have

1, History of head injury in the previous few weeks;

2, Drowsiness, confusion and headache more than anticipated from the severity of the neurological deficit;

3, Fluctuating course of symptoms and

4, History of intake of anticoagulants.

If the stroke onset was clearly sudden, but there was no obvious focal deficit, then brain imaging will show a thalamic or cerebellar infarct or hemorrhage.

Other diagnosis to be considered

Multiple sclerosis - young age

Peripheral nerve or root lesion - clinical signs useful.

Post-seizure hemiparesis – history helpful.

Metabolic encephalopathy - global rather than focal neurological features.

Somatization and hysteria - young age

Encephalitis - fever, clinical symptoms and signs, diffusely abnormal EEG.

Intracranial abscess - fever and predisposing cause such as otitis media, sinusitis and congenital heart disease etc.

MIDDLE CEREBRAL ARTERY- SUPERFICIAL TERRITORY INFARCTS

Superficial branches of the middle cerebral artery (MCA) form distal to the origin of lenticulostriate arteries. As they run in the subarachnoid space, they are called pial branches. They give the cortical, subcortical branches to frontal, parietal and temporal lobes after the MCA trunk and divide in to two (upper and lower) or three (upper, middle and lower) divisions.

Because of characteristic feature of the pial artery network that is with multiple extensive anastomoses, multiple distal emboli are necessary to produce infarction.

The etiology of embolism is large-artery disease (>50%) in internal carotid artery (ICA) or MCA occlusion in one third of the patients or cardiac disease in one quarter of the patients.

INFARCTS IN THE TERRITORY OF THE DEEP PERFORATORS FROM THECAROTID SYSTEM

In comparison to the pial artery network, the deep perforators originated from the distal ICA or the MCA are terminal branches that perforate the basal part of the cerebral hemispheres. For that reason, occlusion of one or several perforators always causing an infarct usually is small. These small deep infarcts are called as Lacunar infarct which are caused by

1. Microatheromatous or lipohyalinotic process associated with chronic arterial hypertension,
2. Small hemorrhage or
3. Dilatation of periarteriolar space.

Embolism to the MCA trunk is a particularly common cause of complete lenticulostriate territory infarction [large striata capsular infarcts]. The artery of Heubner from the anterior cerebral artery (ACA) and the

anterior choroidal artery from the carotid siphon are not only perforators, because they also supply cortical territories.

ANTERIOR CEREBRAL ARTERY INFARCTS

ACA territory infarcts are less common than MCA infarcts by 20-30 times. ACA, pial territory infarct cause mutism at the onset, crural hemiparesis, transcortical motor aphasia, frontal tasks impairment, grasp reflex, unilateral left apraxia, mood disturbance and incontinence. Simultaneous bilateral ACA infarction can occur due to the common origin of both ACAs. Symptoms will be akinetic mutism, incontinence and bilateral grasp reflex.

BORDER ZONE CEREBRAL INFARCTS

Infarction develops at the level of the extra territorial border zone between two main pial arterial branches. Those are commonly called watershed infarcts. They usually occur between the ACA and MCA territories anterior water shed infarcts or between the MCA and posterior cerebral artery (PCA) territories –posterior water shed infarcts.

Anterior water shed infarcts

Subcortical infarcts produce hemiparesis, predominating in the lower limb, with transcortical motor aphasia when lesion is on the left. Cortical infarcts produce proximal brachial hemiparesis. Bilateral anterior watershed cortical infarcts cause bi-brachial paralysis (man-in-the-barrel).

Posterior watershed infarcts give picture that is similar to that of posterior MCA pial infarcts except for a more common occurrence of transcortial sensory aphasia.

Bilateral watershed infarcts often have a symmetrical pattern. Sudden and profound hypotension cause bilateral infarcts in posterior boundary zones.

A simple system separates stroke patients into four main clinical syndromes: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS), and posterior circulation syndrome (POCS). This division depends entirely on the symptoms and signs.

Next, CT or MRI brain imaging separates the patients with primary intra cerebral hemorrhage. Subsequently, based on community based studies infarctions shown by imaging are divided into four types

Total anterior circulation infarct, about 15% of the total (TACI) [28 29];

Partial anterior circulation infarct, 35% (PACI) [31];

Lacunar infarct, 25% (LACI) [32]; and

Posterior circulation infarct, 25% (POCI).

This classification gives some idea about prognosis, residual disability, and the chance of recurrence, and the cause of the stroke [29].

TOTAL ANTERIOR CIRCULATION SYNDROME [TACS]

It is a characteristic clinical syndrome consisting of

1. Contralateral hemiparesis with or without sensory deficit, involving the whole or at least two of three body areas (face, upper limb and lower limb)
2. A homonymous visual field defect and
3. A new higher cortical dysfunction (Dysphasia, neglect, visuospatial problems etc., depending on cerebral dominance).

Often patients are drowsy that any cognitive and visual field defects have to be assumed.

A large hematoma in one cerebral hemisphere or a massive infarct can affect the cortex[25], basal ganglia and internal capsule and cause total anterior circulation syndrome. A large hematoma may cause midline shift, transtentorial herniation and coma within a day, whereas these changes need two to three days to evolve in massive infarct for cerebral edema to develop.

PARTIAL ANTERIOR CIRCULATION SYNDROME [PACS]

This clinical syndrome consists of

1, only two of the three components of total anterior circulation syndrome [TACS], or

2, Isolated cortical dysfunction such as dysphasia or

3, Predominant proprioceptive deficit in one limb.

PACS is usually caused by occlusion of a branch of middle cerebral artery usually as a consequence of embolism from heart or proximal arteries. PACS is also caused by lobar hemorrhage.

LACUNAR SYNDROME [LACS]

Lacunar syndromes are due to the lesions affecting the corona radiata, internal capsule, thalamus, cerebral peduncle, and pons.

The four main lacunar syndromes are

1. Pure motor deficit:

It is a unilateral motor deficit involving two of three areas (face, arm, leg). There are often sensory symptoms but no signs. The lesion is in internal capsule or pons. it makes about 50% of lacunar strokes.

2. Pure sensory stroke:

Symptoms are sensory loss. It has the same distribution as pure motor stroke. The lesion is in thalamus. It is about 5% of lacunar strokes.

3. Sensorimotor stroke:

Lesion is usually in thalamus or internal capsule. It averages about 35%.

4.Ataxic hemiparesis:

It is about 10% of all lacunar strokes. It is a combination of corticospinal and cerebellar lesions. Symptoms include dysfunction affecting arm and leg, dysarthria and clumsy hand.

POSTERIOR CIRCULATION SYNDROME

Combination of brainstem, cerebellar, thalamic, or occipital lobe signs indicate significant infarction in the supply of the vertebrobasilar circulation, or a localized hemorrhage. Presence of both brainstem and

occipital lobe signs is highly suggestive of infarction due to thromboembolism within the basilar and posterior cerebral artery (PCA) territories.

Proximal PCA occlusion causes enough temporal, thalamic and midbrain infarction to cause some contralateral hemiparesis and sensory loss with marked cognitive deficit such as aphasia, as well as homonymous hemianopia, causing confusion with occlusion of the middle cerebral artery or its branches. It is the so-called 'walking total anterior circulation syndrome (TACS) because though it fulfills the definition of a TACS, the motor weakness is very mild.

THALAMIC STROKE:

Infarction or hemorrhage of thalamus is uncommon. Thalamic stroke syndrome consists of paralysis of upward gaze, small pupils, depressed consciousness, disorientation, aphasia and impairment of verbal memory.

CEREBELLAR STROKE:

Cerebellar stroke is also uncommon. Extensive infarction or hemorrhage causes vertigo, nausea, vomiting, horizontal nystagmus, incoordination, ipsilateral and truncal ataxia, as well as dysarthria. Some will have often brain stem signs.

IMAGING OF THE BRAIN

COMPUTERISED TOMOGRAPHY

ISCHEMIC STROKE: The CT appearance of cerebral infarction is mostly time dependent. Though CT findings for ischemic stroke can be detected within 6-8 hours of onset, CT can be normal up to 24 hours.

CT findings in hyper acute infarct:

- Can be normal in 50-60% cases
- Hyper dense artery seen in 25-50%
- Obscuration of lentiform nuclei can be seen.

CT findings in acute Infarct

- Loss of sulcal effacement
- Loss of grey and white matter interfaces
- (insular ribbon sign obscuration of cortico medullary border)
- Low density basal ganglia

CT findings after 1-3days of infarct

Increasing mass effect

- Wedge shaped low density area that involves both grey and white matter[26]
- Hemorrhagic transformation may occur.

CT findings after 4 days to 1 week

- Gyral enhancement
- Mass effect,
- Edema persists

After 1-8 weeks

- Contrast enhancement persists
- Mass effect resolves

CT findings after months to years

- Encephalomalacic changes
- Volume loss
- Rarely calcification

Early findings on CT may be effacement of adjacent subarachnoid spaces and loss of grey and white matter contrast enhancement. By 24 hours, the abnormal low attenuating area becomes clearly seen. Characteristically insular ribbon sign is defined as an early specific sign of MCA infarction. Early findings on non- contrast CT will be development of cytotoxic edema.

CT scan through the suprasellar will show hyper intense MCA. It is indicative of thrombus within the artery.

Combination of cytotoxic and vasogenic edema causes mass effect and decreased attenuation. Cytotoxic edema causing mass effect is

maximum between 3-10 days, and may lead to herniation. Mass effect completely clears by 3 weeks.

LACUNAR INFARCTION:

Because of the small size, CT may miss the lacunar infarct. Lacunar infarcts are secondary to arterial diseases which affect the deep penetrating vessels of brain. These arteries may show very small foci of sclerosis caused by micro atheroma or lipohyalinosis.

MAGNETIC RESONANCE IMAGING OF STROKE [27]:

Earliest MRI findings are vascular flow related abnormalities. These include absence of normal flow and slow flow with intravascular arterial enhancement. These signs can be seen within minutes of symptoms onset. Intravascular enhancement is seen nearly in 75% of acute cortical infarcts. Other early MRI findings will be hyper intense signal on T2 weighted images, which may not be seen within 8 hours. On both initial and follow up examinations the TI weighted images are sensitive. Acute infarcts are identified and diagnosed more on MRI as compared to CT.

Course and Prognosis.

Several factors influence the immediate prognosis in cerebral thrombosis. In the case of very large infarcts, swelling of the infarcted tissue may occur, followed by displacement of central structures and tentorial

herniation. Smaller infarcts of the inferior surface of the cerebellum can cause foramen magnum herniation and death. In basilar infarction associated with deep coma, the mortality rate is around 40 percent.

Prognosis of ischemic stroke patients is better by

1. Keeping the airway clear,
2. Controlling brain edema,
3. Preventing aspiration pneumonia, and
4. Maintaining fluid and electrolyte balance.
5. Control of respiratory and urinary infections.

With smaller infarcts, the mortality is around 3 to 6 %.

Paralyzed muscles are flaccid in the first some days or week after stroke. Gradually spasticity appears, and the tendon reflexes appear more brisker. Posture of arm is in flexed adducted position, and the leg assumes an extended position.

On the other hand, early development of spasticity in the arm or the early appearance of a grasp reflex may predict a favourable prognosis.

In some individuals with massive temporoparietal lesions, the hemiplegia remains flaccid. If the internal capsule is not damaged completely in a stroke but it involves the lenticular nucleus or thalamus then the patients will have

hemichorea, athetosis, tremor, or ataxia, depending upon the particularly the lesion. Bowel and bladder control usually returns normally.

Often the hemiplegic limbs are at first tender and ache on manipulation. Physiotherapy should be initiated early to prevent contractures of muscles and periarthritis of the shoulder, elbow, wrist, knuckles, knee, and ankle. Sometimes atrophy of bone and pain in the hand may accompany the shoulder pain (shoulder-hand syndrome).

Feeling of dizziness and unsteadiness of gait often persists in case of damage to the vestibular system in brainstem infarcts. Recurrent seizures are relatively uncommon in thrombotic strokes. But they are about 20% in embolic cortical infarcts. When multiple infarcts occur over a long period, patients will have multi-infarct dementia.

Starkstein et al found out that fatigability and depression are more common in strokes that involve the left frontal lobe.

FIBRINOGEN

In haemostatic system, fibrinogen is a main protein. At the end stage of clotting, thrombin changes soluble fibrinogen into fibrin monomers, which polymerize to a fibrin clot which is insoluble. At last, fibrinogen promotes platelet adhesion and aggregation via the αIIbβ3 integrin, thus inducing blood coagulation. Fibrinogen is also involved in platelet aggregation, regulation of Factor XIII activity and inflammatory reactions. Fibrinogen also plays a role

in other physiological reactions including fibrinolysis, cellular and matrix interactions, wound healing and neoplasia.

Fibrinogen is a major determinant of blood and plasma viscosity. Raised fibrinogen levels predict future vascular events.

In plasma, concentration of fibrinogen is between 2 and 4 mg/mL (6 - 12 μM), and its half-life is about 3-4 days. Fibrinogen is a plasma glycoprotein that is mainly synthesized by liver hepatocytes. Fibrinogen is an acute phase reactant, it is up regulated two to eight times by interleukin 6 (IL-6) and steroids during the acute-phase response to inflammation, infection and tissue injury. The fibrinogen levels varies with environmental and genetic factors, age, gender, BMI, race, season, smoking, physical exercise, diet and use of several drugs.

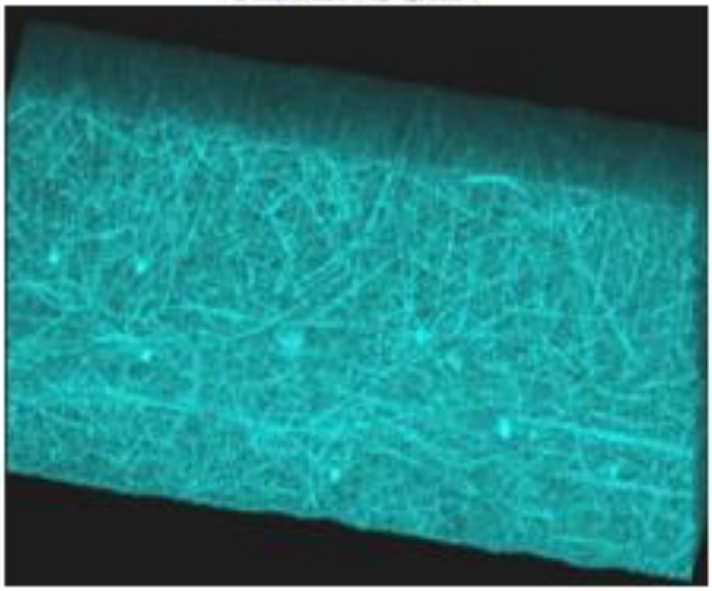
Structure of fibrinogen

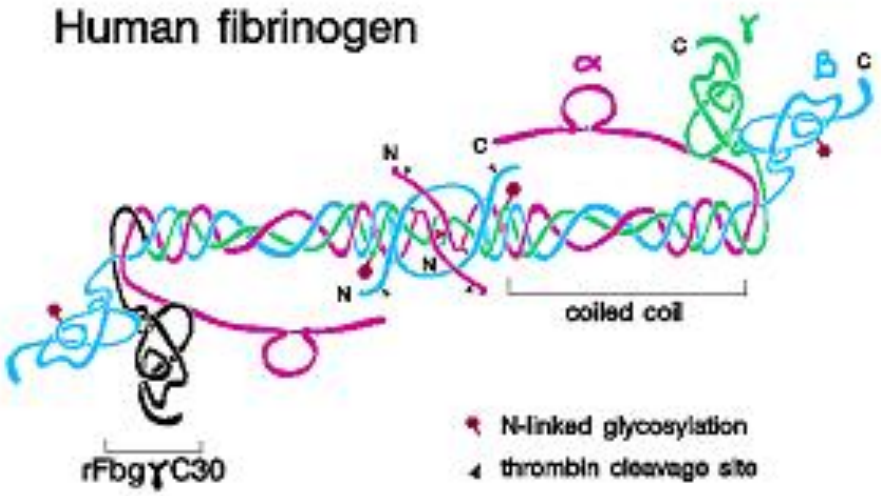
Fibrinogen molecules are elongated 45 nm structures. It consists of one central E region connected by α-helical coiled-coil segments to 2 peripheral D regions. The fibrinogen molecule comprises two sets of identical disulfide-bridged halves. Each half consists of three polypeptide chains termed Aα, Bβ and γ. These six polypeptide chains assemble to make hexamer (AαBβγ) 2, joined together with 29 disulfide bonds. The fibrinogen molecule has at least 12 domains, which are grouped into three major regions E, D and C regions. Both D and E regions has binding sites for fibrin assembly, cross-linking and platelet interactions. The two C regions are involved in fibrin assembly, activation of factor XIII, modulation of fibrinolysis and cell adhesion.

The common human fibrinogen molecule has 2964 amino acids and molecular weight of approximately 340 kilo Dalton (kDa). The Aα, Bβ and γ polypeptide chains have of 610, 461 and 411 amino acids with molecular weights of 68 kDa, 55 kDa and 49 kDa respectively. The 3 polypeptide chains Aα, Bβ and γ are encoded individually by the fibrinogen alpha (FGA), fibrinogen beta (FGB) and fibrinogen gamma (FGG) genes, which are clustered in a region of approximately 50 kilobases (kb) and they are located on chromosome 4q 23-32.

The central domain consists of a dimeric structure in which each dimer has the three amino terminals of the individual arms. The slightly thickened

ELECTRON MICROSCOPIC PICTURE PLASMA FIBRINOGEN





(H. Cole, adapted from R. F. Doolittle)

amino terminal ends of the Aα and Bβ chains indicate fibrinopeptides A and B, respectively. Fibrinopeptide A and B will not be seen in fibrin. The dimeric halves of the central domain are joined together by three of 11 disulfide bonds. The rest of disulfide bonds are seen between the Aα and Bβ chains and in the junctions between the central domain and the coiled-structures. These coiled-structures are made up of the single Aα, Bβ and γ chains super coiled as -helices. Six disulfide bonds in each coiled structure are reason for the super coil structure. They attached to the central and lateral domains in the form of disulfide rings. The basic structure consists of three pairs of polypeptide chains: α, β and γ, arranged like a mirror image. The amino acid residue arrangement is such that the inside of the coiled structure is hydrophobic and the outside of coiled structure is polar.

Each lateral domain have a mass of 67, 200 Da. Each domain is represented by random folds of the γ and β lobes. There are four carbohydrate clusters, each 2,500 Da. Two are placed on each lateral domain on the β chain and two located on each arm in the γ chain, near the central domain. TheAα polar appendage is the site of primary cross-linking. It is close to the carboxyl terminal of the γ chains.

Fibrinogen is degraded by plasmin yielding key fibrinogen fragments. It is a physiologic process that normally occurs in vivo. In the laboratory, plasmin digestion gives a group of fragments originally called as fragments

A, B, C, D and E as determined by diethylaminoethyl chromatography. The fragments are labeled according to the order in which they form from the process. The intermediate products are called as Fragment X and Y. The X fragment is formed from breaking one of the coiled-coils midway between the central and lateral domain. It yields fragments D and Y. Further cleavage of fragment Y gives fragments D and E.

Plasma fibrinogen is synthesized exclusively by the hepatocyte, and the synthesis of the fibrinogen is under the coordinated control of three separate genes located on chromosome 4. Subsequently by assembly of the constituent polypeptide chain and the addition of carbohydrate side chains, the mature fibrinogen molecule is produced and secreted into the circulation. It has a half- life of 4 days and it has a fractional catabolic rate of 25% per day.

Role of fibrinogen in three major functional processes.

1. Conversion of soluble fibrinogen into insoluble fibrin during the process of blood coagulation.

2. Activation of fibrinolytic system: The polymerized fibrin uses as a template for the localized assembly and activation of the fibrinolytic system, which modulates fibrin deposition and clot dissolution and

3. Fibrinogen binds and supports platelet aggregation and to endothelial cells, where it plays a role in tissue repair.

Conversion of fibrinogen to insoluble fibrin –

It can be divided into three distinct phases

1. Thrombin cleaves fibrinopeptide by enzymes.
2. Polymerization of fibrin,
3. Factor XIII stabilizes fibrin by covalent cross-linking.

Fibrin formation[53]

Thrombin breaks the Arg 16 Gly 17 bond of the Aα chain and the Arg 14 gly 15 bond of the Bβ chain. It results in the release of two molecule of fibrinopeptide A and two of fibrinopeptide B per molecule of fibrinogen. It forms fibrin monomer, which consists three chains called as the α, β and γ chains.

Though thrombin does proteolytic cleavage of FP-A and FP-B simultaneously, under physiological conditions, the cleavage of FP-B doesnot lead to fibrin formation. Nuclear magnetic resonance and x-ray crystallographic studies show that thrombin bind to a discrete segment of the N-terminal of the Aα chain of fibrinogen. Thrombin also binds to fibrin

through a non-catalytic site called as fibrinogen recognition site, which binds to the N- terminus of the β chain.

In intact fibrinogen, fibrinopeptides which are negatively charged play a role in maintaining the dispersion of individual fibrinogen molecules. Because next to their cleavage by thrombin, the resulting fibrin monomers polymerize spontaneously.

F**ormation of protofibril**

Polymerization of fibrin monomers involves the reciprocal non-covalent interaction of molecular determinants in the frequent E region of an adjacent fibrin monomer. The resulting dimer is arranged in a half staggered overlap. Dimer continues to grow in length by the staggered addition of fibrin monomers. It results in the formation of two-stranded, half staggered polymer referred to as **a protofibril**, the basic structural unit of the fibrin clot. The final stage of fibrin formation is characterized by the factor XIIIa which forms covalent amide bonds between the E-amino group specific lysine residues and γ CONH2 groups of glutamine residues. These covalent bonds are first formed between the γ chains of two molecules. The dimerization of the γ chain occurred by bridges between Lys 406 of one γ chain and Glu 398/399 of another. It is then followed by progressive covalent cross-linking of multiple-chains. Cross linking at branch points also produces D-trimers (or) D-tetramers.

Platelet fibrinogen

In addition to plasma fibrinogen, the circulating blood also has very small pool of fibrinogen, which is present with in the platelet as granules. Few studies have shown that the fibrinogen is synthesized by the megakaryocyte, but more investigations showed that both megakaryocytes and platelets are capable of internalizing fibrinogen from plasma by glycoprotein II b/IIIa mediated process. Platelet fibrinogen is deficient of γ chain. Platelet fibrinogen secreted after stimulation plays supporting role in hemostasis.

Heterogeneity of fibrinogen

In healthy individuals, fibrinogen molecule has a high degree of heterogeneity that can occur in more than one million different forms as there are enormous possible combinations of genetic polymorphism, posttranslational modifications, alternative processing of messenger ribonucleic acids (mRNAs), and proteolytic degradation. Abnormal modifications are associated with diseases but more investigations are needed to prove them.

Normal level of plasma fibrinogen is 190-350mg/dl. But fibrinogen levels as low as 50% of normal or minimum 80mg/dl are sufficient for normal coagulation to proceed without any bleeding. Plasma fibrinogen levels more than 350mg/dl can be considered as hyperfibrinogenemia. Normal levels are

varied between different laboratories and different assays. Various methods to measure fibrinogen levels are

1. Clonable gravimetric method
2. Functional method - Clauss
3. Automated Nephalometric method
4. ELISA - Enzyme Linked Immuno Sorbent Assay.

ELISA is a highly specific test. It does not cross react with early products of fibrinogen degradations and can detect even one intact A chain of fibrinogen. It is suitable for estimation of fibrinogen after thrombolytic therapy. But functional methods are widely used especially Clauss method.

High fibrinogen is also influenced by genetic factors. Fibrinogen levels are under genetic control. About 20-50% inter individual variations in the fibrinogen levels were explained by genetic polymorphisms in fibrinogen gene. Most common polymorphism is - 455G > A in the promoter region of FBG-. It is strongest genetic variants associated with ischemic stroke in certain populations. Various studies revealed that FBG - gene was associated with raised fibrinogen levels.

HYPERFIBRINOGENEMIA

Plasma fibrinogen more than 350mg/dl can be considered as hyperfibrinogenemia.

Plasma fibrinogen levels rises significantly with age, with habits such as smoking, and in certain conditions such as hypertension, obesity and diabetes mellitus. Even, among normal individuals the plasma fibrinogen levels varies and although the exact reason is unknown. Recent studies tell that fibrinogen levels may be genetically controlled. High plasma fibrinogen levels have been observed in normal persons having a special nucleotide sequence polymorphism at the 5' untranslated region of the Bβ chain. It seems to be a rate limiting step in fibrinogen biosynthesis. Increased transcription of this gene also results in elevated fibrinogen levels in a minority of the population.

In contrast, in most individuals fibrinogen plays as an acute phase reactant protein. Therefore it levels varied according to inflammation. In inflammations, the release of IL6 by macrophages results in increase in transcription of Bβ gene. It produces raised levels of fibrinogen. Elevated fibrinogen levels in ischemic stroke within 48 hours are not due to acute phase reaction.

Lip et al[50] reported that peak value of plasma fibrinogen occurred about 1 to 2weeks after onset of ischemic stroke. Tamamy et al [52] found that

onset of peak of acute phase reactant fibrinogen and CRP was at about third day. Study of STAT & ESTAT showed that fibrinogen levels didn't show significant rise till 5 days. Fibrinogen levels were monitored 3 hourly intervals in initial 12hr and every 12hr till day 5 of stroke. At baseline mean fibrinogen was 250mg/dl and at end of fifth day it was 210mg/dl and there was no significant elevation in the first five days.

Genetic polymorphism located within the IL-6 responsive element plays an important role in causing elevated fibrinogen levels in different individuals. This is distinct from the polymorphisms in the 5'untranslated region described above. The raised concentration of plasma fibrinogen has important clinical role, as indicated by several studies showing that hyperfibrinogenemia is an independent risk factor in stroke and in IHD. High Plasma fibrinogen concentration in the population increases the risk of CVD threefold as compared with those in the normal range of fibrinogen. Plasma fibrinogen level of one standard deviation (SD) (0.6 mg/ml) above the mean significantly multiplies the risk of CVD. When other risk factors for CVD and stroke such as age, sex, smoking, high BP, diabetes and serum cholesterol were considered, high levels of fibrinogen still emerged as an important risk factor.

Plasma fibrinogen has been demonstrated in atherogenesis and in arterial thrombus formation. Many studies have shown a significant impact of

fibrinogen on cardiovascular disease incidence including stroke. Fibrinogen was also positively associated with many of the common risk factors for stroke including age, sex, smoking, hypertension, obesity and diabetes.

Studies enlightening fibrinogen as a significant risk factor for ischemic stroke

Edzard Ernst and Karl Ludwig et al[23] stated that fibrinogen can be viewed as a major cardiovascular risk factor and can be related patho physiologically related to vascular events after studied 92147 subjects.

A study conducted with 30 acute ischemic stroke patients & 30 acute ischemic stroke patients & 30 controls. Lipid profile, Plasma fibrinogen, platelet aggregation were estimated. They found that collagen induced platelet aggregation and plasma fibrinogen significantly higher in cases. No significant difference was seen in triglyceride, VLDL and HDL cholesterol & atherogenic index among cases & controls. There was also positive correlation between atherogenic index & fibrinogen.

AizhongGu and K.Sree Kumaran Nair et al stated that there was a strong association existed between atherosclerotic disease and fibrinogen levels and plasma concentrations of fibrinogen raised with age. This study also concluded that the raised levels of fibrinogen were due to a slower rate of disposal of fibrinogen rather than increased production rate.

Hazra B, Sengupta N, Saha SK et al[37] in their study on plasma fibrinogen in stroke, explained that the increased plasma fibrinogen may be a significant risk factor for the thrombotic ischemic stroke. Koenig et al[36] described the evidence on the pathogenetic role of fibrinogen in various vascular beds.

Thavaraj V; BehariM; Prasad K, et al[38] did blood viscosity studies were in 14 patients with acute stroke, 8 with cerebral infarction, 6 with cerebral hemorrhage and thirteen controls and observed a statistically significant higher values of plasma and whole blood viscosity in patients with acute stroke than in normal controls suggesting that the hemorrheological factors play an important role in the pathophysiology of stroke patients. They found out that plasma fibrinogen levels were statistically higher ($P<0.01$) in patients than in normal controls.

Qizilbash et al[35] identified importance of fibrinogen in two prospective observational studies. He found out that the association between fibrinogen & ischemic stroke were independent of other hemostatic and hemorrheological factors (VWF, Tissue Plasminogen activator and PCV) & plasma fibrinogen was the most important potentially treatable risk factor in ischemic stroke patients. Study supported accelerating influence of fibrinogen on atherosclerosis. Individuals with high fibrinogen but without any other risk factors should be considered for therapies to reduce fibrinogen levels.

Bo Kristensen, JanMalm&Colleagues[45] Sweden found out increased fibrinogen levels & tissue plasminogen activator mass concentration were independently associated with ischemic stroke in young patients.

Lee , Lowe GD, M Woodword et al[33] the related plasma fibrinogen to family history of premature heart disease, personal history of hypertension, diabetes, stroke and coronary heart disease. This large population based study showed that plasma fibrinogen levels are raised in patients with family history of premature heart disease and with personal history of hypertension, diabetes and obesity.

Studies supporting fibrinogen as a good predictor of outcome of ischemic stroke

EUROSTROKE [UK, Finland and Rotterdam] large cohort study showed that raised fibrinogen is a good predictor of stroke in 202 stroke patients and did not disclose a differential relation with fatal or nonfatal stroke or with type of stroke whether hemorrhagic or non-hemorrhagic stroke.

Kim JH, Shin D.J, Park KH and his Colleagues[39] in Korea conducted prospective study & evaluated that a raised level of plasma fibrinogen associated with large artery atherosclerosis (LAA) in acute ischemic stroke and with a poor clinical functional outcome.

WojcechTuraj and Agnieska Slowik et al[40] compared plasma fibrinogen in patients with acute ischemic stroke and found that large vessel disease more significantly associated with high plasma fibrinogen than with small vessel disease.

Zhu – Yi Cheng, Li Ying, Beijing et al[41]evaluated 116 patients & found out that high fibrinogen in acute ischemic stroke predicted poor outcome.

YezhuLycui Bi Hua conducted a case controlled study with 131 ischemic stroke patients & 148 controls and found out that high fibrinogen was a risk factor and significantly correlated with subtypes of ischemic stroke.

Peter M Roth well. Sally.C.Howard, Dermot A Power, Sergei A.Gutnikov and others[43] studied 3 prospective studies of patients with TIA or minor ischemic stroke and found out that risks of acute ischemic stroke & TIA events increased linearly with elevated fibrinogen levels.

A placebo controlled, randomized clinical trial study of patients from Bezafibrate infarction prevention study concluded that plasma fibrinogen was a strong predictor of subsequent stroke rather than direct causative factor among the patients at increased risk.

MistryP.P, ChawlaK.P.RaiH.PJaiswal.P.P [43] studied 56 patients of stroke and found that high serum fibrinogen was present significantly among the stroke patients.

Wojciechturaj, AgnieshaSlowik, Tomasz Dziedzic Mateusz Adamski, Jack Strojny, Poland[44] conducted a study to establish the significance of hyperfibrinogenemia as a possible predictor of 30 day and 1 year mortality in ischemic stroke patients and concluded that raised concentration of plasma fibrinogen shortly after ischemic stroke independently (>3.5g/L) increased risk of death within one year after ischemic stroke.

Another study with 185 patients having mild cognitive impairment showed that hyperfibrinogenemic had increased risk of dementia &vascular dementia.

A study was conducted in 56 patients of acute ischemic stroke & 42 age & sex matched controls. Study showed mean plasma fibrinogen in patients 326.45 mg/dl -significantly higher than the control group. Smoking was described as a significant predictor of predictability of 36.7% for elevated serum fibrinogen. They adjusted other risk factors & at the end they found that plasma fibrinogen was found to be significantly high in patients compared to controls $p < 0.001$. They concluded that fibrinogen was a powerful predictor of ischemic stroke and did not predict the type and prognosis of stroke.

Northwick Park Heart study included white men 40 – 64years and tested for clotting factors including fibrinogen. Fatal coronary events and fibrinogen were significantly associated independent of other risk factors. Northwick Park Heart study included white men 40 – 64years and tested for clotting factors including fibrinogen. Fatal coronary events and fibrinogen were significantly associated independent of other risk factors. About 15 of 24 died of IHD had fibrinogen level > 3.2g/L.

Speedwell study showed that fibrinogen levels measured by two different methods were associated significantly with IHD & its risk factors.

Caterphilly speed well collaborative heart disease studies revealed strong association of smoking with fibrinogen and the fibrinogen as a strong independent risk factor.

Gothenburg study - About 81% of target population [aged mean 54 years] followed for 13.5 years. There were about 60 deaths, 37 strokes & 92 myocardial infarctions Analysis ended that blood pressure and fibrinogen were risk factors for ischemic stroke and fibrinogen, smoking & cholesterol as risk factors for ischemic heart disease. This study was extended now to 21year follow up and there were 333 deaths, 119 myocardial infarctions and 81strokes. Conclusion of the study was fibrinogen was strongly statistically associated with stroke and mortality rate.

Leigh study: Totally 505 men aged 40-69 years were followed up for 7.3years. 40 cases of MI occurred. Fibrinogen was positively associated with MI incidence. When patients also had hypertension, incidence of MI was about six fold higher when associated fibrinogen levels more than 3.5g/L. Multivariate analysis showed predictive power of all risk factor variables in ascending order LDL, no of cigarettes smoked per day, obesity, cholesterol, blood pressure, age and at top of order plasma fibrinogen. Certain drawback of the study was highly selected population. It included only 76% of target population.

Framingham study showed a stepwise increase in fibrinogen with smoking dose. 14 year follow up of patients showed increased incidence of risk for cardiovascular disease with raised fibrinogen levels in heavy smokers.

PROCAM [prospective cardiovascular munster study] study[23] investigated 2817 patients of age 40-65years with no history of MI or stroke. About 55 Cardiovascular events occurred in 1674 men in 4 years follow up period. 29 of 55 events were having fibrinogen in upper terfile.

GRIPS [Gottingen Risk Incidence and Prevalence] study - a prospective cohort study[23] included 40 - 60 year aged men free of cardiovascular disease. About 107 myocardial infarctions occurred after 5 year follow up. Results showed fibrinogen a strong predictor in cardiovascular events. This study

showed LDL had weak relationship with event occurrence but it was statistically significant.

Cumulative analysis from six prospective epidemiological studies (Gothenburg, Framingham, PROCAM, Northwick park heart study, GRIPS) showed that fibrinogen is an independent cardiovascular risk factor considering various study designs, sample composition, follow-ups & target points[23].

A prospective study examined fibrinogen in 120 patients who had myocardial infarction. Reinfarction took place in patients with fibrinogen level more than 7.5g/L.

In a conducted study, out of 1716 men, who had MI followed for 2 year, about 126 patients had developed further ischemic events. They were found to have elevated fibrinogen which is statistically significant.

Fibrinogen levels rise after an acute ischemic stroke. Earlier it was thought that elevated fibrinogen was due to an acute phase reaction due to brain necrosis. But now studies proved that fibrinogen levels significantly increased in patients with TIA where no infarction took place. It indicates that fibrinogen levels are elevated before stroke.

Since there is significant increased risk of cardiovascular and cerebrovascular diseases associated with increased levels of plasma

fibrinogen, the significant value of lowering fibrinogen in the primary as well as secondary prevention of atherosclerotic disease is now recognized as an important topic for global research.

National Institutes of Health stroke scale [55, 56]

The **National Institutes of Health Stroke Scale** [NIHSS] is a tool for assessing stroke severity and as an excellent predictor for patient outcomes. The NIHSS is composed of 11 items, each item ranges between 0 and 4. Score 0 means normal. Score 4 is indicating severe degree of neurological impairment. The maximum score is 42 and the minimum score is 0.

Total score 21-42 indicates severe stroke. Score of 1-4 is minor stroke. Score of 5-15 is moderate stroke and 16-20 is moderate to severe stroke. **It consists of 11 items containing level of consciousness, horizontal eye movement, visual field defect, facial palsy, motor arm, motor leg, limb ataxia, sensory, language, dysarthria and extinction and inattention**

Always patient's first response to the task should be taken except language assessment where his best effort can be recorded

The NIHSS is a standardized and repeatable assessment tool in ischemic stroke patients utilized by large clinical studies. Consistency of NIHSS scores has been excellent in inter-personnel and in test-retests. NIHSS is then repeated at regular intervals. Follow up of scores can be used to

monitor the treatment methods and evaluate patient's improvement or decline.

Rapid assessment of stroke severity by NHSS scoring reduces treatment delay of tissue plasminogen activator therapy. Current standard recommendation for treatment of acute ischemic stroke is tissue plasminogen activator therapy [tPA] and should be given within 4.5 hours of onset of stroke. Some neurologists avoid tPA if NHSS score is less than 5.

NHSS is summation of 4 factors i.e. left and right motor function and left and right cortical functions.

Left cortical – loss of consciousness questions & commands and language

Right cortical – horizontal eye movement, visual fields, sensory, extinction

Right motor – right arm motor, right leg and dysarthria

Left motor – left arm motor, left leg.

NIHSS gives more points on defects in the left hemisphere. About 98% of humans have verbal processing take place in the left hemisphere.

The NIHSS gives 7 of the total 42 points for verbal skills; It gives 2 marks for the LOC questions, 2 marks for LOC commands, and 3 marks for the language. NIHSS is a better predictor of lesion volume in the strokes occurring within the left cerebral hemisphere.

NIHSS is found to be an excellent predictor of the patient outcomes. A baseline NIHSS score more than 16 indicates high probability of poor outcome, while NIHSS score less than 6 indicates a high chance of a good

recovery. An increase of 1 point in a patient's NIHSS score decreases the chance of a good outcome by 17%.

The **modified Rankin Scale** [mRS] [58,59]is a very commonly used scale for measuring the degree of disability or dependence in the daily life of people who had ischemic stroke or other causes of neurological disorders, and it becomes the most widely used as functional outcome measure for stroke studies. We can reduce the Inter-observer reliability of the mRS by using a structured questionnaire during the interview.

The scale has a value from 0-6, running from normal health without symptoms to death. Scale of more than 3 indicates poor outcome.

MATERIALS AND METHODS

Setting:

This study was done in the Department of Medicine, Madurai Medical College and Government Rajaji Hospital, Madurai.

Period of Study:

From April 2012 to October 2012.

Design of study:

This is a prospective study of patients admitted with acute ischemic stroke new onset in Government Rajaji Hospital, Medicine Department Madurai.

Sample Size:

50 patients with acute ischemic stroke admitted in the Department of Medicine, Government Rajaji Hospital, Madurai and 50 age and sex match controls were taken.

Inclusion Criteria:

All patients presented with acute stroke with definitive signs of neurological deficit and ischemic stroke was proved by CT brain. Hemorrhagic stroke was ruled out.

Exclusion criteria:

1. Patients with cerebral hemorrhage
2. Individual with acute infection and inflammatory episode
3. Patients with valvular heart disease
4. Patients on anticoagulant therapy
5. Patients with severe liver disease, renal failure
6. Patients with absent peripheral pulses
7. Pregnancy and Puerperium
8. Women on oral contraceptive pills
9. Patient's undergone surgery within 3-6 months

METHODS:

Patients with acute ischemic stroke admitted in the medicine department were enquired about presenting complaints, mode of onset of neurological deficit, past history of TIA, hypertension, diabetes mellitus in detail. Special enquiry about alcoholism, smoking, pregnancy or recent delivery and use of anticoagulants or oral contraceptives was made. Any similar illness in the family was asked. BMI was identified. Complete general examination and neurological examination was done. Optic fundus was seen in all cases to identify papilledema, diabetic retinopathy and hypertensive retinopathy. Other systems were examined in detail.

Basic investigations such as Hb, blood cell count, urine for albumin, sugar deposit, blood sugar, and urea serum creatinine and serum electrolytes total cholesterol were estimated. Electrocardiography, echocardiography and CT scan of brain were done.

Serum samples for plasma fibrinogen estimation were taken after confirming ischemic stroke & sent to the laboratory. MRI brain was also taken if the CT brain was normal and if the patient was affordable. Other risk factors such as history of TIA, MI, SHT, DM and BMI & serum cholesterol were taken into account. NIHSS [National Institute Health Stroke Scale] Score at the time of admission were calculated. Patients are categorized into three groups [NIHSS<6, 6-14 and >14]. Standard treatment was given to all patients with ischemic stroke. They were adequately treated with anti edema measures, antiplatelets (aspirin alone), antibiotics, good nursing care and good physiotherapy. After 8 weeks of onset of stroke, all the patients were again followed up. Functional outcome were determined by use of Modified Rankin scale (MRS). All patients were stratified using MRS Scale [0-2,3-4 and 5-6] into three groups .

Plasma fibrinogen level was correlated with NIHSS score at the time of admission and again with functional outcome using MRS score. Patients with MRS score of 5 and 6 were declared as very poor outcome & MRS of 3 and 4

as poor outcome. Patients with MRS 0, and 1 were considered as good outcome.

METHOD OF ASSAYING FIBRINOGEN IN PLASMA (CLAUSS METHOD)[48]

Normal plasma fibrinogen level ranges from 190 to 350mg/dl. However the level more than 350mgs% can be considered as a risk factor as far as cerebrovascular disease is concerned.

Fibrinogen was estimated by functional assay (clauss method) manually.

First step is to dilute plasma (1:10) to minimize the effect of plasma inhibitory substances such as heparin, FDP etc. Diluted citrated plasma is made clotted using high concentration of thrombin (100 u/l) and now new coagulation time is directly proportional to the fibrinogen concentration.

Testing process requires plasma (standard reference) with known level of fibrinogen measured against a well-known international standard. A graph is made using reference plasma by making serial dilutions (1:10 - 1:40) in buffers to give fibrinogen concentrations. Clotting time of each of these dilutions is found out and it is platted on [clotting time / fibrinogen] log - log graph paper. 1:10 concentration is 100% normal.

Test sample platelet poor diluted plasma (1:10 buffer) incubated 37^{o} C, phospholipid, thrombin & calcium are added. Time taken for clot to form was noted in calibration curve and from the curve fibrinogen level was deducted.

STATISTICAL ANALYSIS:

The figures collected were recorded in a master chart. Statistical analysis was done using epidemiological package 2002 developed for WHO. KruskallWallis 'Chi' square test was used to see significance. A 'P' value less than 0.05 was taken to indicate significant difference among the variables. Pearson correlations were done between fibrinogen and NIHSS score and then with MRS value. Two tailed test was applied and significant P value <0.05 was considered as good correlation.

OBSERVATIONS

Table – 1

Age Distribution

Comparing incidence to age.

Age in years	No. of patients	Percentage	Male / Female
< 40	4	8	3 / 1
41 – 50	13	26	11 / 2
51 – 60	17	34	13 / 4
61 – 70	13	26	8 / 5
> 70	3	6	3 / 0

In age group 31- 40 there were 4 patients 3 male & one female.

There were 13 patients in age group constituting 26 % in the age group 41-50 years.

In age group 51-60 there were 17 patients - (13 male & 4 female) making 34% of total cases

In 61-70 year age group, 26% of total cases i.e. (13 patients) which have 8male & 5 female had ischemic stroke.

Above 70yr age group only 3 male patients are there.

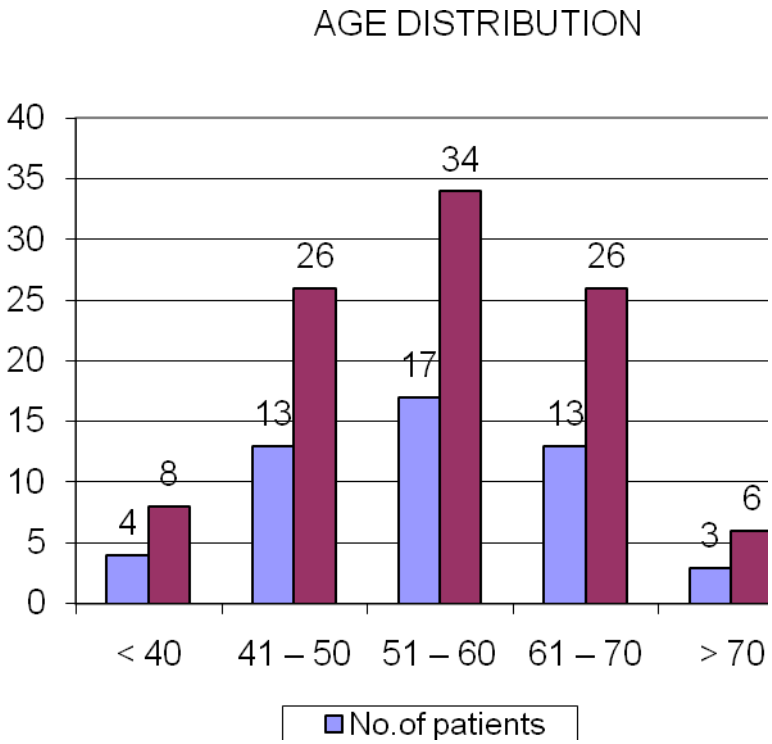

AGE DISTRIBUTION
40
35
30
25
20
15
10
5
0
4
8
13
26
17
34
13
26
3
6
< 40
41 – 50
51 – 60
61 – 70
> 70
No.of patients

Table-2

INCIDENCE WITH RELATION TO SEX

Comparing incidence with sex

Sex	NO.OF PATIENTS	PERCENTAGE
Male	38	76%
Female	12	24%

Amounting 50 cases about 38 patients are males & 12 female constituting 76% & 24% respectively.

SEX DISTRIBUTION

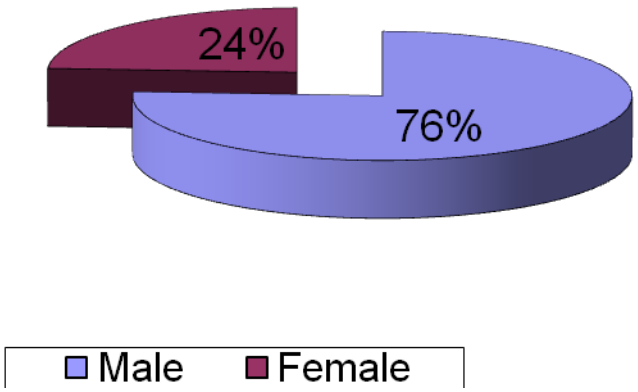


Table-3

HISTORY

Significant history

HISTORY	NO.OF PATIENTS
Diabetes	23
Hypertension	22
Smoking	28
Alcoholism	16
TIA	8
MI	14

In our study, 23 persons are suffering from DM constituting46%. About 22 persons associated with SHT. about 28 individuals are smokers it is about 56%. 16 of the 50 patients are alcoholic [32%]

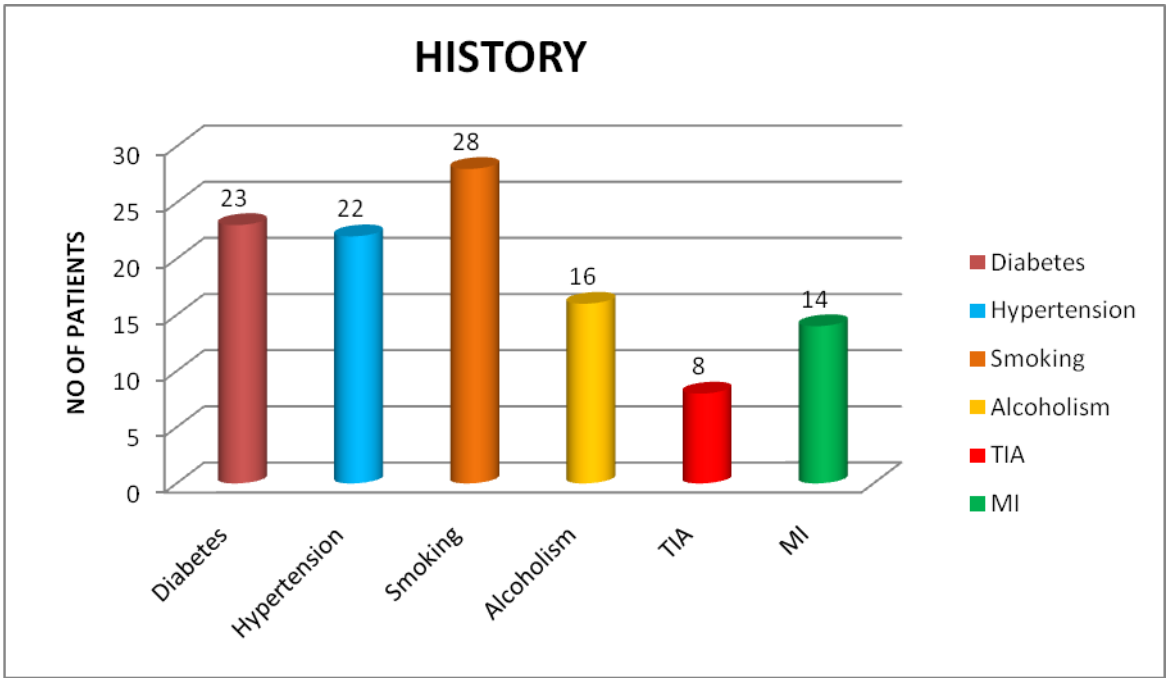

HISTORY
NO OF PATIENTS
30
25
20
15
10
5
0
23
22
28
16
8
14
Diabetes
Hypertension
Smoking
Alcoholism
TIA
MI
Diabetes
Hypertension
Smoking
Alcoholism
TIA
MI

Table -4

INCIDENCE OF SYNDROMES

SYMPTOMS	NO. CASES	MALE	FEMALE	PERCENT
TACS	7	5	2	14
PACS	19	14	5	38
LACS	15	12	3	24
POCS	9	7	2	18

Total anterior circulation syndrome constituted about 14%. Partial anterior circulation syndrome made up of 38%. Posterior circulation syndrome was about 18%. About24% of cases had lacunar syndrome.

Table-5

AGE AND FIBRINOGEN

Age Group	Cases		Control	
	Mean	SD	Mean	SD
31-40	411.3	115.7	195	35.1
41-50	389.6	135.6	216.1	58.6
51-60	402.6	120.9	278.3	67.1
61-70	391.2	120.6	265	80.1
>70	448.3	63.3	341	40.3
P Value	0.955 Not significant		0.011 Significant	

Our study showed relationship between age & plasma fibrinogen in cases was statistically not significant [p = 0.955] and on the other hand it is significant in control [p = 0.011]. (<0.05)

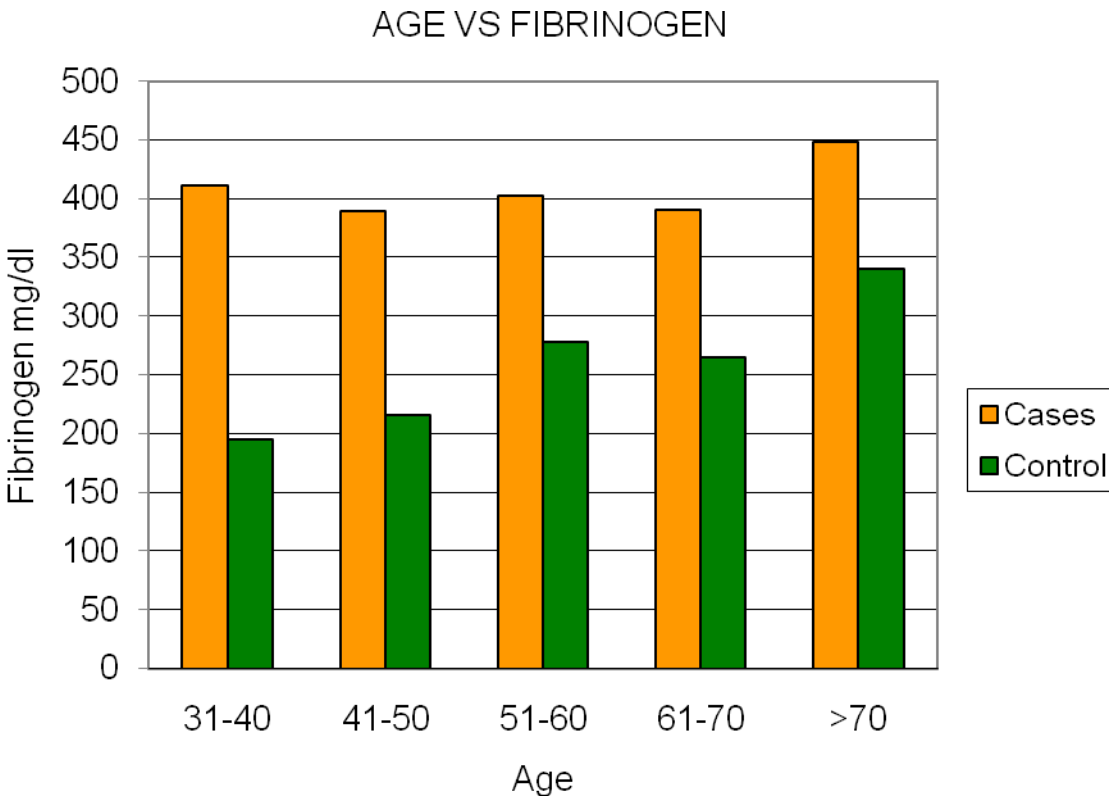

AGE VS FIBRINOGEN
500
450
400
350
300
250
200
150
100
50
0
Fibrinogen mg/dl
31-40
41-50
51-60
61-70
>70
Age
Cases
Control

Table-6

SEX AND FIBRINOGEN

Sex	Cases		Control	
	Mean	SD	Mean	SD
Male	404.3	119.4	276.8	11.9
Female	384.2	119.1	199.1	10.5
P Value	0.612		0.002	

In our study, no statistically significant difference between sex and plasma fibrinogen level in cases is established (P =0.612). But in control there is statistically significant difference exists (P=0.002).

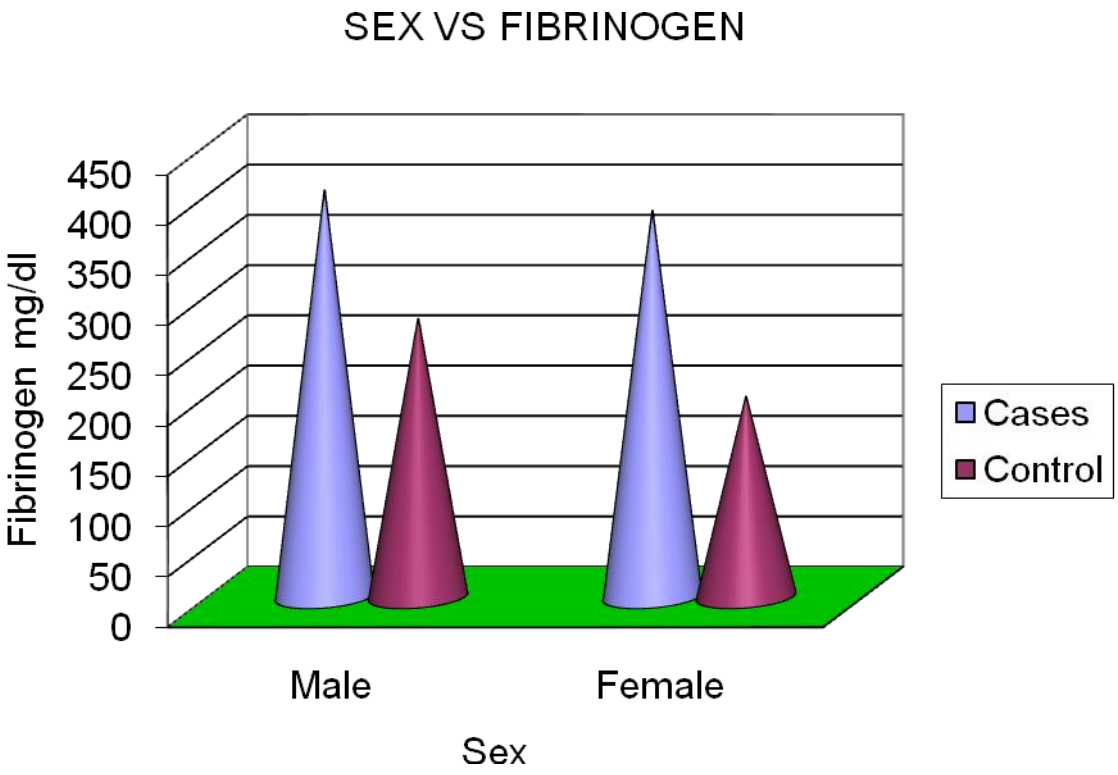

SEX VS FIBRINOGEN
Fibrinogen mg/dl
450
400
350
300
250
200
150
100
50
0
Male
Female
Sex
Cases
Control

Table-7

DM AND FIBRINOGEN

DM	Cases		Control	
	Mean	SD	Mean	SD
Diabetes	383.9	96.3	313.4	65.7
Non Diabetes	412.8	134.9	217.5	50.6
P Value	0.396 Not significant		<0.001 significant	

In the study, relationship between diabetes & non-diabetics in cases was not statistically significant (P = 0.396). But in controls relationship is statistically significant (p = < 0.001).

Table-8

FIBRINOGEN IN DM OF CASES VS CONTROLS

DM	FIBRIOGEN	
	Mean	SD
CASES	383.9	96.3
CONTROLS	313.4	65.7
P Value	0.007 Significant	

This table shows that there is statistically significant difference in plasma fibrinogen among cases and controls. (p = 0.007)

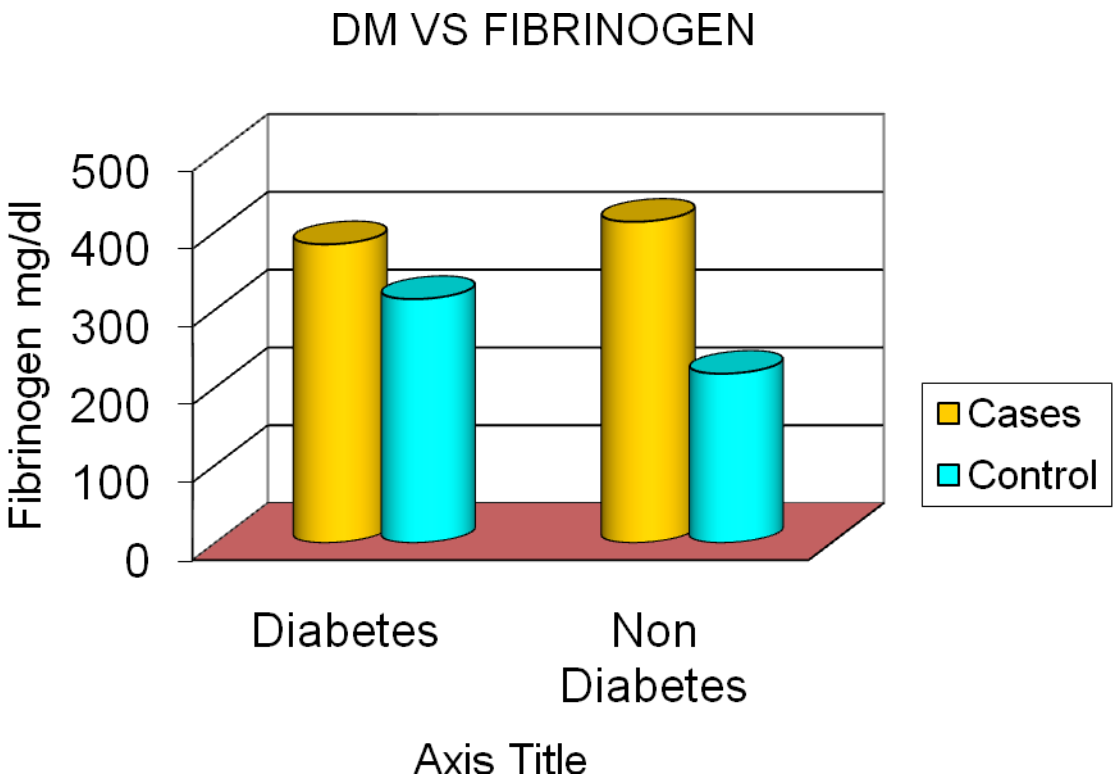

DM VS FIBRINOGEN
Fibrinogen mg/dl
500
400
300
200
100
0
Diabetes
Non Diabetes
Axis Title
Cases
Control

Table-9

HYPERTENSION AND FIBRINOGEN

HT	Cases		Control	
	Mean	SD	Mean	SD
HT	428.4	105.6	286.5	78.2
Non HT	376.8	124.8	245.9	70.1
P Value	0.127 Not significant		0.068 Not significant	

This table shows there is no statistically significant difference in plasma level of fibrinogen in hypertensive & non-hypertensive of both cases (p 0.127) controls (p -0.068).

Table-10

FIBRINOGEN AND HYPERTENSION CASES vs. CONTROLS

Hypertension	FIBRIOGEN	
	Mean	SD
CASES	428.4	105.6
CONTROLS	286.5	78.2
P Value	<0.001	

In our study, plasma fibrinogen statistically significantly associated with hypertensive patients in cases and controls (P = < 0.01).

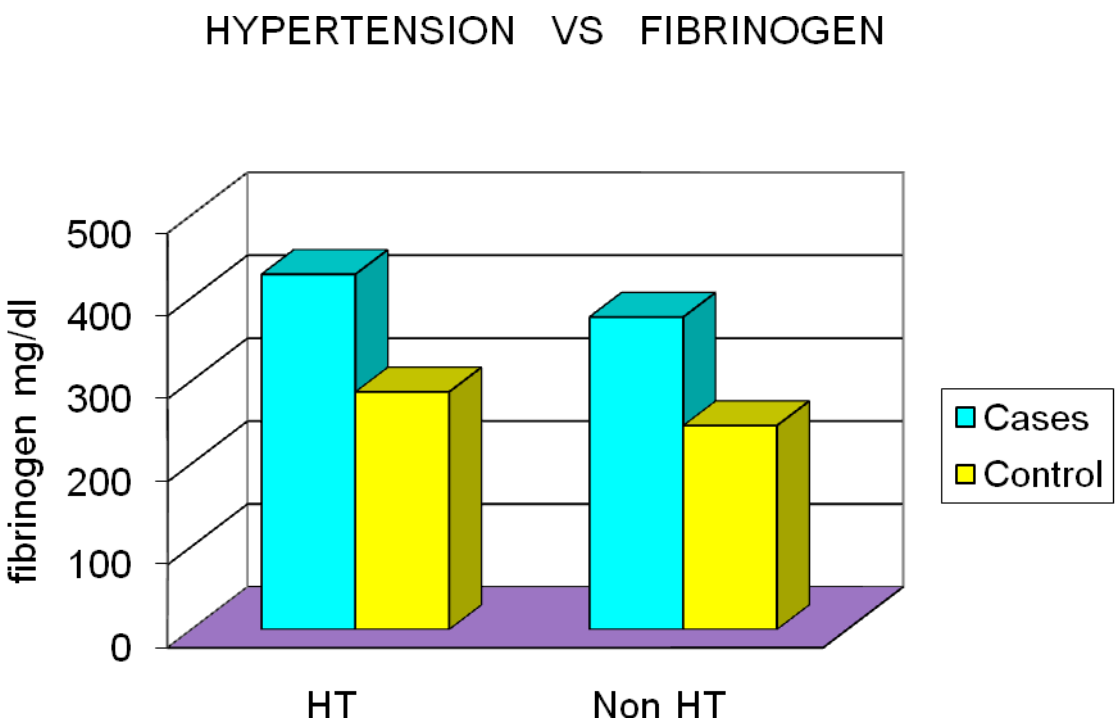

HYPERTENSION VS FIBRINOGEN
fibrinogen mg/dl
500
400
300
200
100
0
HT
Non HT
Cases
Control

Table-11

SMOKING AND FIBRINOGEN

Smoking	Cases		Control	
	Mean	SD	Mean	SD
Smokers	419.6	126.6	245.6	72.9
Non smokers	373.8	104.4	246.1	69.6
P Value	0.178 Not significant		0.986 Not significant	

No statistically significant difference in smoking and nonsmoking among cases & controls (P= 0.178) and (P = 0.986) respectively.

Table-12

FIBRINOGEN IN SMOKING CASES Vs CONTROLS

GROUP	FIBRIOGEN	
	Mean	SD
CASES	419.6	126.6
CONTROLS	245.6	72.9
P Value	<0.001	

Fibrinogen level shows statistically significant difference among smokers of cases & controls (p <0.001).

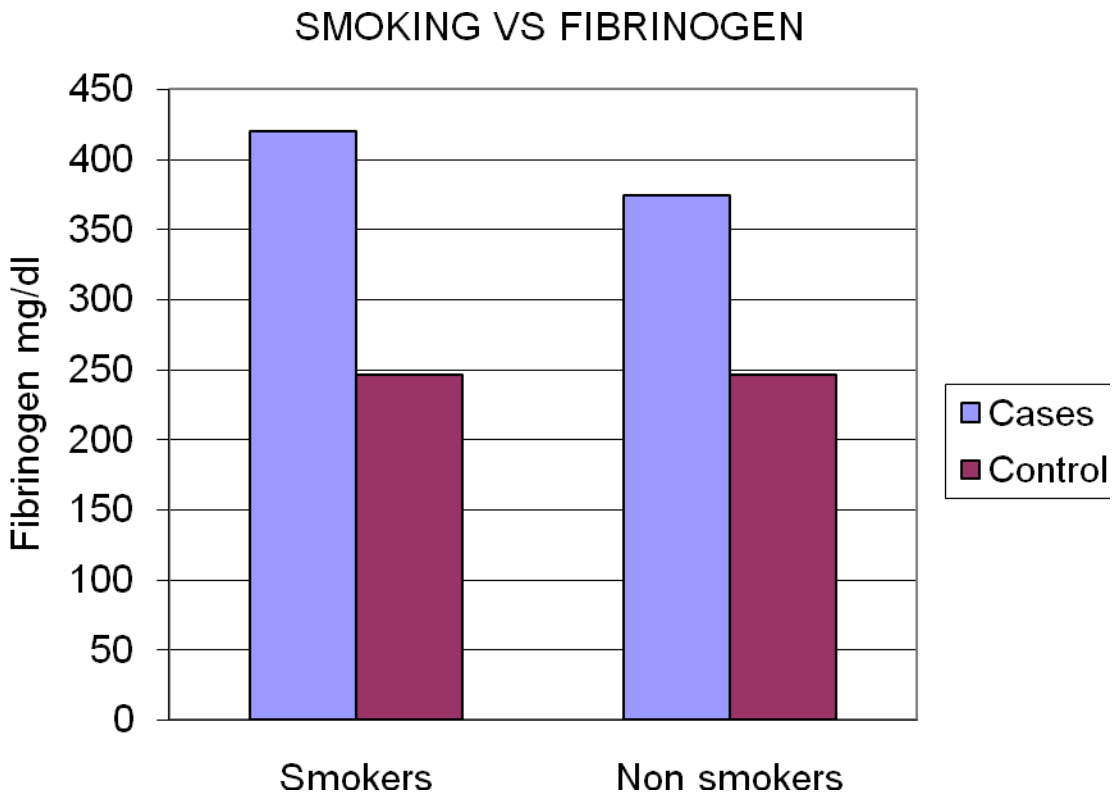

SMOKING VS FIBRINOGEN
Fibrinogen mg/dl
450
400
350
300
250
200
150
100
50
0
Smokers
Non smokers
Cases
Control

Table-13

ALCOHOLISM AND FIBRINOGEN

	Cases		Control	
	Mean	**SD**	**Mean**	**SD**
Alcoholic	**424.4**	**121.3**	**289.7**	**83.2**
Non alcoholic	**387.8**	**117.1**	**241.3**	**63.5**
P Value	**0.313 Not significant**		**0.024 significant**	

There is no significant difference between alcoholic and non alcoholic with fibrinogen among cases P=0.313 but there is significant difference among controls P=0.024

Table 14

ALCOHOLISM

CASES VS CONTROLS

Alcoholic	**Fibrinogen**	
	Mean	**SD**
CASES	**424.4**	**121.3**
CONTROLS	**289.7**	**83.2**
P Value	**< 0.001 Significant**	

There is statistically significant difference P<0.001 existing between cases and controls for alcoholism.

Table-15
CHOLESTEROL AND FIBRINOGEN

Cholesterol	Cases		Control	
	Mean	SD	Mean	SD
<200mg/dl	385.2	127.0	245.7	66.4
>200mg/dl	416.3	107.9	323.4	81.0
P Value	< 0.001 Significant		0.004 Significant	

In our study, among cases & control there was statistically significant difference in plasma fibrinogen in patients with hypercholesterolemia > 200mg & normal cholesterol levels.

Cases - $P < 0.001$

Controls $P= 0.004$

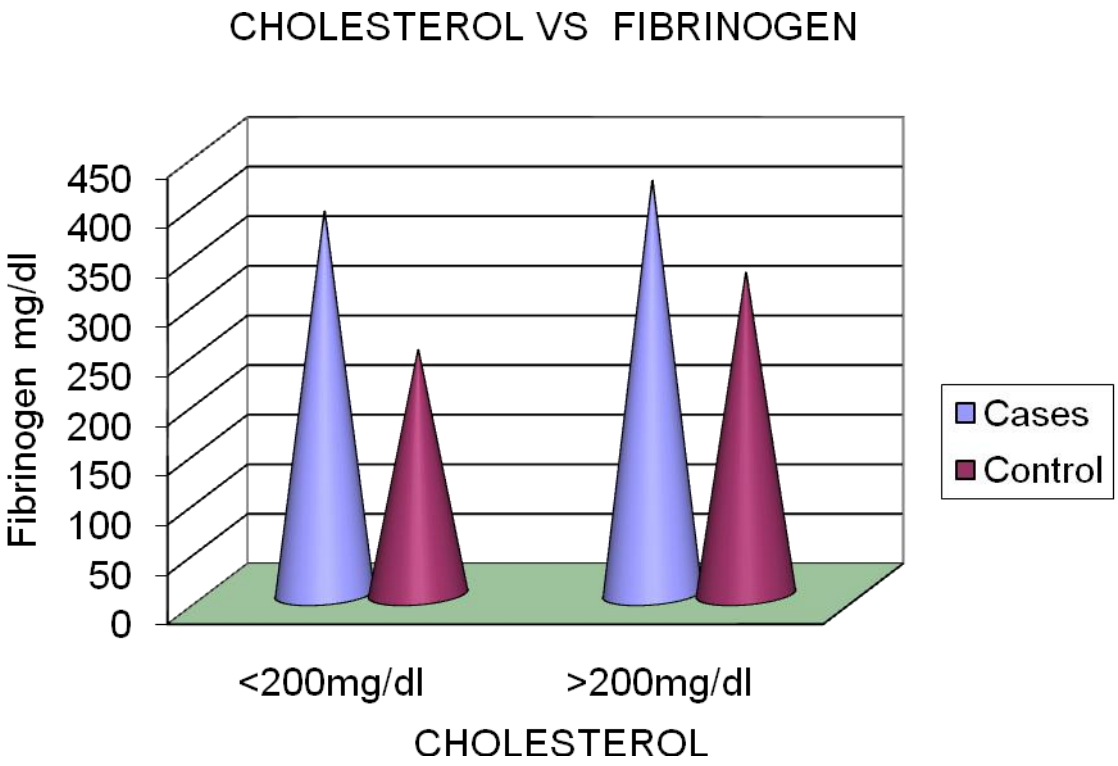

CHOLESTEROL VS FIBRINOGEN
Fibrinogen mg/dl
450
400
350
300
250
200
150
100
50
0
<200mg/dl
>200mg/dl
CHOLESTEROL
Cases
Control

Table-16

FIBRINOGEN IN HYPERCHOLESTROLEMIA

GROUP	FIBRIOGEN	
	Mean	SD
CASES	416.3	107.9
CONTROLS	323.4	81.0
P Value	0.027 Significant	

Fibrinogen levels are statistically significant in hypercholesterolemia patients in cases & controls (P 0.027).

Table-17

BMI AND FIBRINOGEN

BMI	Cases		Control	
	Mean	SD	Mean	SD
<25	353.65	97.2	233.65	58.1
25-30	401.76	106.3	350.6	55.9
>30	564.29	65.8	326.3	74.2
P Value	<0.001 Significant		<0.001 Significant	

There was statistically significant difference in obesity (BMI>25) & plasma fibrinogen level

Cases – (P<0.001) Controls- (P 0.001)

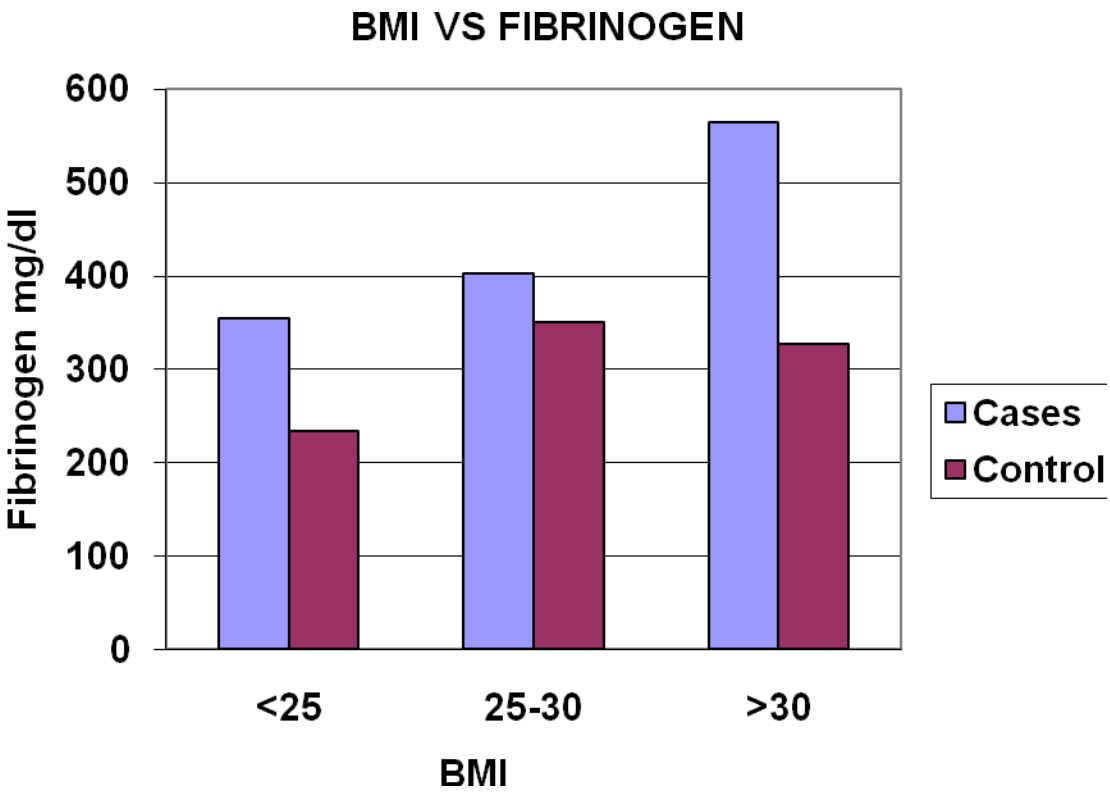

BMI VS FIBRINOGEN
600
500
400
300
200
100
0
Fibrinogen mg/dl
<25
25-30
>30
BMI
Cases
Control

Table-18

FIBRINOGEN AND OBESITY

CASES Vs CONTROL

GROUP	FIBRINOGEN	
	Mean	SD
CASES	449.2	121.2
CONTROLS	342.5	60.3
P Value	0.007 Significant	

There was a statistically significant difference between cases & controls with increased BMI. (P=0.007)

Table-19

FIBRINOGEN IN CASES Vs CONTROL

GROUP	FIBRINOGEN	
	Mean	SD
CASES	399.5	118.5
CONTROLS	259.7	74.7
P Value	<0.001 Significant	

Fibrinogen levels in cases and controls showed statistically significant difference among case and controls (P<0.001).

Table-20

NIHSS Score vs. FIBRINOGEN

NIHSS	FIBRINOGEN	
	Mean	SD
<6(10)	297.5	51.4
6-14(17)	367.3	99.7
>14(23)	467.6	112.1
P Value	<0.001 Significant	

About 23 patients had severe neurological deficit NIHSS>14 and they had mean fibrinogen=467.6mg/dl. About 10 patients had mild form of deficit NIHSS<6 and they had mean fibrinogen=297.5mg/dl. About 17 patients had mean fibrinogen of 367.3 mg/dl with NIHSS 6-14.

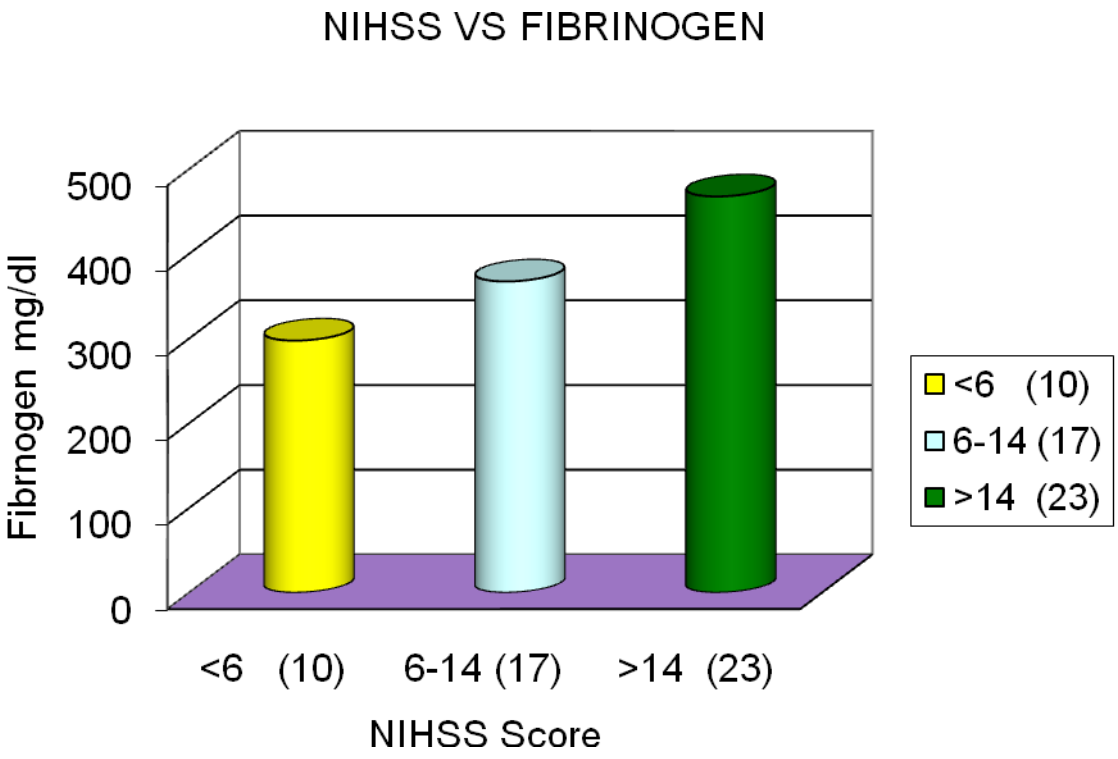

NIHSS VS FIBRINOGEN
Fibrnogen mg/dl
500
400
300
200
100
0
<6 (10)
6-14 (17)
>14 (23)
NIHSS Score
<6 (10)
6-14 (17)
>14 (23)

Table 21

CORREELATION

Serum fibrinogen		NIHSS
	Pearson coefficient	0.7415
	Two tailed T - P	0.000
	(significant)	
	n	50

Serum fibrinogen levels are significantly correlated with NIHSS Score by Pearson correlation(r=0.7415) and had significant P value =0.000.

Table-22

MRS Vs. FIBRIONOGEN

MRS	FIBRINOGEN	
	Mean	SD
0 – 2 (28)	356.4	101.9
3, 4 (20)	439.2	111.9
5 (2)	605.0	21.2
P Value	0.001 Significant	

About 28 patients are categorized in MRS scale 0-2 and mean fibrinogen is 356.4mg/dl. Only 2 patients are in the severe degree of disability MRS scale 5 with mean fibrinogen of 605mg/dl. About 20 patients are in MRS 3and 4.

MRS VS FIBRINOGEN

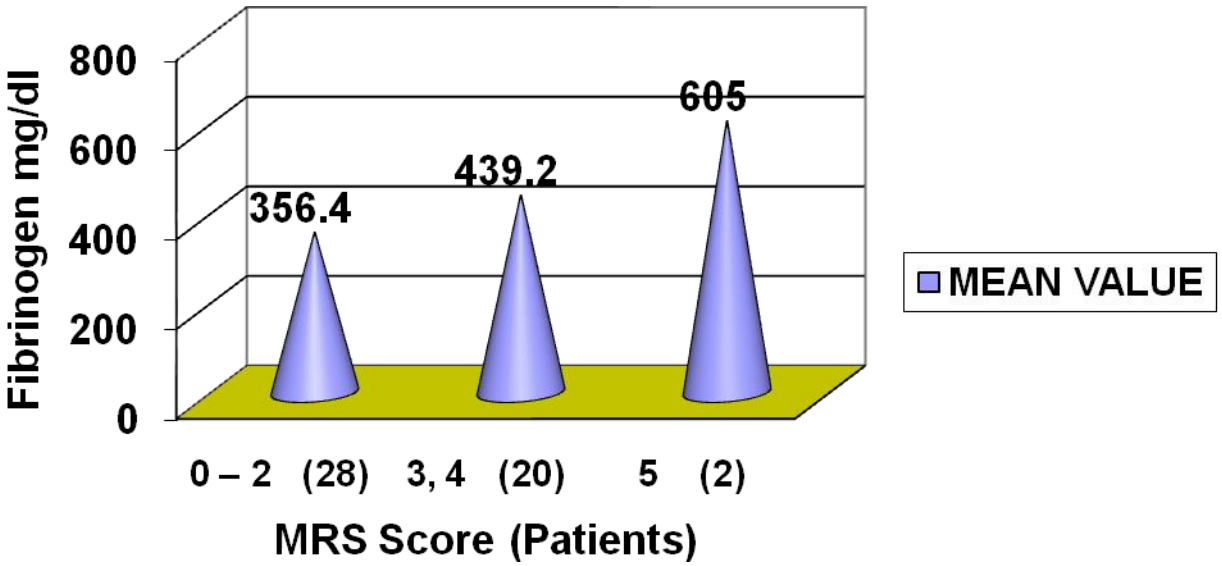


Table 23

CORRELATION

Serum fibrinogen		Modified Rankin scale
	Pearson's coefficient	0.5165
	Two tailed test P	0.0001
	Significant	
	N	50

Serum fibrinogen values are statistically correlated with modified Rankin scale by Pearson correlation r=0.5165 and two tailed test P=0.0001

DISCUSSION

In our study population of 50 patients, the age of patients ranged from 30 years to 75 years. There were 4 patients in age group of 31 to 40 includes 3 male and 1 female. There were 13 patients in 41 to 50 age group includes 9 males and 2 females. In the age group of 51–60 there were 17 patients of which 13 were male 4 were female. 13 patients in the age group of 61-70 of which 8 were males and 5 were females and 4 male patients. In the age group of more than 70 only 3 male patients are there. In those 50 patients 38 were male 12 were female patients indicating a male predominance. The incidence of major vascular risk factors was analyzed, Diabetes mellitus was found in 46% of the patients. Hypertension was found in 44% of the patients. Smoking was present in 56% of the patients. Alcohol intake was present in 32% cases. History of coronary artery disease was present in 28% of the patients previous history of TIA was present in 16% of patients hypercholesterolemia found in 46% of the patients. BMI more than 25 found in 21 cases.

Total anterior circulation syndrome constituted about 14% [7 cases]. Partial anterior circulation syndrome made up of 38% [19 cases]. Posterior circulation syndrome was about 18% [9 cases]. About 24% of cases had lacunar syndrome [12 cases]. Plasma fibrinogen level was significantly increased with age advance in the control group [361mg/dl above 70 years]

not in the cases. Male has high plasma fibrinogen value [276.8 vs. 199.1 mg/dl] than female in the control group significantly.

Plasma fibrinogen level was elevated in hypertension [428.4 vs 286.5mg/dl], diabetes [383.9 vs 313.4mg/dl], obesity [449.2 vs 342mg/dl] and hypercholesterolemia [416.3 vs 323mg/dl]. This finding is supported by Pai Mahesh et al[34] and Lee et al study.

About 23 patients had NIHSS score of more than 14 at the time of stroke which indicates the severity of stroke. They had mean fibrinogen 467.6mg/dl. About 10 patients had mean fibrinogen 297.5 mg/dl and NIHSS <6 with mild neurological deficit. Only two patients had initial fibrinogen value of more than 600mg/dl and they had MRS scale of 5 after 8 weeks of stroke indicating very severe disability and outcome. About 20 patients had initial plasma fibrinogen at the time of stroke with mean value of 439.2 mg/dl and they had moderate disability after 8 weeks with MRS 3 and 4. 28 patients had MRS score of 0 and 1 after 8 weeks of stroke indicating no disability or very mild form of disability. These 28 patients had mean fibrinogen at the time of admission was 356.4mg/dl.

AizhongGu and K. Sree Kumaran Nair et al stated that plasma concentrations of fibrinogen raised with age. This finding is present in our study significantly in controls.

Grazilla Bruno, et al stated type 2 diabetic patients had a high prevalence of hyperfibrinogenemia and fibrinogen increased with age in men. This study supports our study. In our study diabetic patients had fibrinogen 383.9mg/dl than controls 313.4mg/dl. Amanda J Lee, Gordon D Lowe, Mark[33] in Scotland found that after adjustment for age, body mass index, and smoking, 74 male and 58 female diabetic individuals had higher serum fibrinogen concentrations than non-diabetic subjects.

Pai Mahesh.C, Chandrasekhara P. et al[34] studied the correlation between plasma fibrinogen levels and other major risk factors to ischemic stroke. This study compared 50 patients (proved to have cerebral infarction by CT scan) were compared with 50 controls. They were adjusted with respect to age and sex. Plasma fibrinogen was high among the males and increases with age. It was high significantly in diabetics when compared to non-diabetics. It was also statistically significant higher value in hypertensive and smokers. Hyperfibrinogenemia is associated with stroke recurrence and TIA. In our study plasma fibrinogen level was significantly increased in smoking, hypertension, diabetes, obesity and hypercholesterolemia..

Another study conducted with 30 acute ischemic stroke patients & 30 acute ischemic stroke patients & 30 controls. Lipid profile, Plasma fibrinogen, platelet aggregation were estimated. They found that collagen induced platelet aggregation and plasma fibrinogen significantly higher in

cases. No significant difference was seen in triglyceride, VLDL and HDL cholesterol &atherogenic index among cares & controls. There was also positive correlation between atherogenic index & fibrinogen. It supports our study in which patients with cholesterol more than 200mg/dl had fibrinogen (mean – 416.3 mg/dl) raised levels compared to the patients with normal cholesterol (mean fibrinogen – 385.2mg/dl).

Gregoy del Zoppo &David.E.Levy&Colleagues[60] analyzed placebo treated data from STAT (Stroke Treatment with Ancrod Trial) & ESTAT (European Stroke Treatment with Ancrod Trail)[47]. Fibrinogen level was estimated within 3 hours or 6hours of stroke. Functional outcome was estimated by Barthel Index Score at 90 days. Multiple logistic regression analysis was used. Fibrinogen levels increased from 340mg/dl (pretreatment) to 24 hour median value of 376mg/dl. Fibrinogen levels were classified as <350mg/dl, 350-450mg/dl, >450mg/dl. Good functional outcome was not produced in patients with high initial fibrinogen > 450mg/dl. In our study 22 patients who had high initial fibrinogen mean value above 439mg/dl suffered severe disability with MRS score of 3 and above. Our findings coincided with Gregoy del Zoppo study[60].

STAT study showed that only 38 patients with high fibrinogen > 450mg/dl having good functional outcome at 90 days were 19.2%. About 212

Patients with lower initial fibrinogen <450mg/dl was 32.1% and they had good outcome.

ESTAT study[47]: 92 placebo treated patients had fibrinogen >450mg/dl. Out of 92 patients, the proportion of patients with good functional outcome at 90 days was 21.6%.About 523 patients with initial fibrinogen (<450mg/dl) had good functional outcome was higher 42%. It was statistically significant (P=0.0006). Proportion of patients achieved good outcome was more in lowest quartile of fibrinogen & more less in highest quartile. In our study about 28 patients with initial fibrinogen (356.4 mg/dl) had good functional outcome which was 56%. Our study was supported by this studty. Di Napoli et.al[49] described that high fibrinogen level measured within 24 hours were significantly associated with death or new vascular disease. 52% patients who were in the upper tertile of fibrinogen levels had new vascular event. Around only 21.1% patients in the lower tertile had vascular event. But association was not significant with a multiple logistic regression analysis that included other risk factors age, initial stroke severity, diabetes and smoking. In our study there was no death and association between fibrinogen and stroke severity, diabetes and smoking was strong.

Lip.et.al[50] stated that no associations were found between mortality at 1 year & fibrinogen levels in ischemic stroke patients.

Roth well et al[42] identified associations was stronger for patient with nonlacunar than lacunar stroke for fibrinogen levels. Even adjusted for age, hypertension, smoking hyperlipidemia association was still significant (p 0.04). In this study hyperfibrinogenemia was more in TACS and PACS compared to lacunar syndrome.

U.Emre.U.Ergun, A.Unal et al[46] studied 43 acute ischemic stroke patients & 37 control individuals. Serum fibrinogen, Ferritin, CRP level, WBC, ESR 24-72hrs were measured. Serum fibrinogen, CRP, ferritin were found out to be increased in cases than in control group.

Delzoppo, David E Levy et al[60] identified independent association of higher initial fibrinogen levels with poor outcome. Study suggested absolute need of treatment to reduce fibrinogen levels in treating acute ischemic stroke. In our study 22 patients who had high initial fibrinogen mean value above 439mg/dl suffered severe disability with MRS score of 3 and above.

NINDS rt PA study[51] [National Institute of Neurological Disorders and stroke] Fibrinogen levels didn't rise at baseline after 2hr of initiation of stroke & 24hrs of onset of stroke. Higher first 24hr plasma fibrinogen levels resulted in 40% relative increase in mortality. In our study two patients had fibrinogen >600mg/dl in the first 24 hours of the stroke and there was no mortality.

High fibrinogen [> 400mg/dl] will make clot thinner and more tightly packed with fibrinogen. Clot will then be very resistant to fibrinolysis. High

fibrinogen is associated with high viscosity. Role of thrombolytic therapy plays a significant role when high fibrinogen levels are detected in early post stroke period.

Gonzalez - Conejero et al[54] evaluated fibrinogen levels in 200 stroke patients and concluded that acute ischemic stroke patients with fibrinogen level > 360mg/dl had poor outcome and also high 3 months mortality. They also suffered severe disability with NIHSS score > 15. Like that, in our study, about 23 patients with fibrinogen value of 467.6 mg/dl had NIHSS >14 and 22 patients with fibrinogen more than 439.8 had poor outcome MRS > 3.

KimJH, Shin DJ, Park KH, & their colleagues[39] studied the functional outcome of ischemic stroke with plasma fibrinogen. Acute ischemic stroke was classified by TOAST classification, into three types [LAA -Large artery atherosclerosis, SVO -Small vessel occlusion, CEO - Cardio embolic occlusion].Serum fibrinogen was taken within 24hours of stroke. National institute of health stroke scale (NIHSS) assessed at admission and 4 weeks later & patients were divided into good group & bad group. Depending on plasma fibrinogen levels, patients were divided into normal group & high group (Plasma fibrinogen > 400 mg/dl).

Out of 619 patients there were 251 patients with LAA. There were 229 patients with SVO. They found that high plasma fibrinogen more than 400 mg/dl ($p < 0.001$) was related to large artery atherosclerosis & high NIHSS

score at admission and significantly related to poor prognosis. They concluded that an elevated level of fibrinogen (> 400mg/dl) significantly associated with larger artery atherosclerosis & poor functional outcome. In our study 22 patients who had high initial fibrinogen mean value above 439mg/dl suffered severe disability with MRS score of 3 and above and had poor outcome.

WojechTuraj, Agnieska slowik et al[40] studied 203 patients. There were 107 patients with small vessel disease and 96 with large vessel disease [LVD]. Fibrinogen level was higher in LVD patients 3.7 g/1 (2.9-4.9g/l) than in SVD -3.2 g/l (2.6-3.4g/l). They concluded that LVD patients with ischemic stroke have high fibrinogen (3.7g/l) & poor outcome.

Zhu Yi cheng, Li-ying et al[41] studied 116 patients with ischemic stroke for 2 years. Various factors such as age, gender, diabetes, hypertension, smoking, and alcoholism and lesion diameter were adjusted. They found that there were no significant difference in fibrinogen between LVD&SVD but high fibrinogen level was seen it large artery atherosclerotic type of ischemic stroke (3.30 ± 1.05g/L) ($p < 0.005$) compared with small vessel disease (2.78 g/l). They concluded that high plasma fibrinogen (3.3±1.05g/l) predicted the functional outcome within one year.

Yczhu, Ly Chi in china et al correlated plasma fibrinogen level with subtypes of ischemic stroke. About 131 cases and 148 controls were selected.

High plasma fibrinogen level (3.09 ± 0.94 g/L) $p < 0.005$ correlated with cerebral infarction at onset of disease. High fibrinogen (3.14 ± 0.81g/l) was significantly correlated with TACI, PACI [total and partial anterior circulation infarction] and posterior circulation infarction [$p < 0.001$] and with extra cranial arteriosclerosis and not with intracranial arteriosclerosis. This study correlated with our findings that high fibrinogen was associated with poor outcome and TACS,PACS and POCS.

Peter.M.Rothwell, Sally.C.Howard, DermotA Power, SerginAGutnikov et al[42]studied 3 prospective studies of patients with TIA. Three trials UK TIA trial (n = 1860), Dutch TIA trial (n-2960) & oxford TIA study (n -293) founded out that high fibrinogen predicted subsequent ischemic stroke with hazard ratio for values above the median of 1.34 (95% CI, 1.13 to 1.60; P = 0.001) & predicted acute coronary events (HR = 1.42 95% CI, 1.18 -1.70, P <0.001) & all ischemic stroke events (HR 1.24 95% CI, 90-1.70 P <0.001) and concluded that risks of recurrent ischemic stroke and acute coronary events increased linearly with fibrinogen level.

About 140 stroke patient & 36 TIA patients from Bezafibrate infarction prevention clinical trial were studied. Plasma fibrinogen was measurement at admission and a year after. Occurrence of stroke was prospectively monitored as an end point. Results were mean fibrinogen were higher among the patients who have CVA (375 vs. 349 mg/dl. $P < 0.001$) &

fibrinogen did not differ significantly by subtypes of CVA. They adjusted for age, blood pressure and other risk factors, high fibrinogen level (375mg/dl) were associated with more than twofold increased risk for ischemic stroke.

MistryP.P, Chawla.K.P, RaiH.P.Jaiswall.P.P. et al[43] estimated serum fibrinogen within 24hrs of ischemic stroke & identified elevated fibrinogen (513.73 ± 74 mg/dl) compared to age, sex matched control group & observed risk in fibrinogen level related to ischemic stroke rather than associated risk factors. Prospective study of 625 stroke patients, measured fibrinogen during rehabilitation period when acute phase response had subsided. Fibrinogen was statistically significantly high in them. Also they had second cardiovascular event within next 2 year. ODDS ratio were significantly raised for fibrinogen (3.67g/l; CI; 1.31 to 11.69) & plasma viscosity (2.86; CI 1.06 to 8.4) independent of other risk factors.

WojciechTuraj, AgnieszkaSlowik, Tomasz Dziezic, MaceuszAdamsk. Jacket Strojny[44], Poland conducted a study in 900 ischemic stroke patients. They analyzed risk factors for stroke, neurological deficit and conscious level on admission and plasma fibrinogen was taken & registered vital statistics at 1, 3, 6, 12 months after stroke. Mean plasma fibrinogen was 2.9g/l. About 25.2 % patients had increased fibrinogen level i.e. >3.5g/L on the first day. Patients with hyper fibrinogenemia were more likely to expire after 1, 3, 6, 12 months than those with normal levels. (21.1 Vs. 15.6%, 36 vs. 24%, 42 vs.

27%, 45 vs. 31%. $p < 0.001$). Hyperfibrinogenemia predicted one year case fatality. Other factors predicted the prognosis were neurological deficit on admission, age, and WBC count and body temperature on day one. These studies predicted outcome like our study.

Bokristensen, Jan malm, Torbjuvn[45] Sweden studied 102 ischemic patients from 1991 - 1996 & 41 controls. Logistic multiple regression analysis showed that plasma fibrinogen was a strong predictor of ischemic stroke (odds ratio 11.25, 95% CI, 3.27 to 38.69).

Studies showed that elevated level of fibrinogen is more significantly commonly associated with vascular dysfunction. At high level, fibrinogen increases cerebrovascular permeability by activating MMP [matrix metalloproteinase]. After fibrinogen infusion into male mice, pialvenular macromolecular leakage increased. This indicates that high fibrinogen damaged micro vascular integrity through activation of MMP -9 and down regulation of VE-Cadherin and up regulation of PV - 1 (plasmalemmal vesicle - associated protein).

Fibrinogen levels rise after an acute ischemic stroke. Earlier it was thought that elevated fibrinogen was due to an acute phase reaction due to brain necrosis. But now studies proved that fibrinogen levels significantly increased in patients with TIA where no infarction took place. It indicates that fibrinogen levels are elevated before stroke.

Lip et al [50] concluded that peak value of plasma fibrinogen occurred about 1 to 2weeks after onset of ischemic stroke. Tamamy et al[52] stated that onset of peak of acute phase reactant fibrinogen and CRP was at about third day. Study of STAT &ESTAT[47] indicated that fibrinogen levels didn't show significant rise till 5 days. Fibrinogen levels were monitored 3 hourly intervals in initial 12hr and every 12hr till day 5 of stroke. At baseline mean fibrinogen was 250mg/dl and at end of fifth day it was 210mg/dl and there was no significant elevation in the first five days. So, in this study plasma fibrinogen was estimated within 48 hours of ischemic stroke after confirming with CT Brain.

CONCLUSIONS

- There is a significant elevation of plasma fibrinogen in ischemic stroke patients compared to the age and sex matched control population.
- Plasma fibrinogen can be used as a significant risk factor for acute ischemic stroke and other vascular events independent of other risk factors.
- Serum fibrinogen levels can also be used as a prognostic indicator and high fibrinogen levels are well correlated with severity and outcome of acute ischemic stroke.
- The primary goal of biomarker plasma fibrinogen in acute ischemic stroke patients should be early identification of high risk individuals who can be targeted for aggressive acute management and improved secondary prevention measures.
- Many secondary prevention interventions like diet, exercise, smoking cessation and drugs [fibrates, omega 3 fatty acids, ticlopidine and pentoxifylline] all will reduce fibrinogen levels and minimize future vascular risk.

FUTURE STUDIES

- **Acute ischemic stroke prognosticator scores should be well defined and well accepted.**
- **Secondary prevention strategies for ischemic stroke patients having fibrinogen level more than 350mg/dl should be analyzed and incorporated.**
- **Clinical cut off points for fibrinogen levels should be standardized.**
- **Long term safety of fibrinogen lowering agents will have to be established.**

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ABBREVIATION

ATP	–	adenosine triphosphate
CBF	–	cerebral blood flow
CMRO2	-	cerebral metabolic rate of oxygen
OEF	-	oxygen extraction fraction
ACA	-	Anterior Cerebral Artery
BMI	-	Body Mass index
CT	-	Computerized Tomography
CVA	-	Cerebrovascular Accident
CVD	-	Cerebrovascular Disease
DM	-	Diabetes Mellitus
FPA	-	Fibrinopeptide - A
FPB	-	Fibrinopeptide -B
HT	-	Hypertension
IHD	-	Ischemic heart disease
MCA	-	Middle cerebral artery
MRI	-	Magnetic Resonance Imaging
TIA	-	transient ischemic attack.
Hs CRP	-	High sensitive C Reactive protein,
sICAM-1	-	Intercellular adhesion molecule soluble forms
LAA	-	Large artery atherosclerosis-
CEO	-	Cardio embolic occlusion
TACS	-	anterior circulation syndrome
PACS	-	partial anterior circulation syndrome
LACS	-	Lacunar syndrome
POCS	-	posterior circulation syndrome
TACI	-	Total anterior circulation infarct
PACI	-	Partial anterior circulation infarct

LACI	-	Lacunar infarct
POCI	-	Posterior circulation infarct
kDa	-	kilo Dalton
FGA	-	fibrinogen alpha
FGB	-	fibrinogen beta
FGG	-	fibrinogen gamma
ELISA	-	enzyme linked Immuno sorbent assay
PROCAM	-	prospective cardiovascular munster study
GRIPS	-	Gottingen Risk Incidence and Prevalence] study
NIHSS	-	National Institutes of Health stroke scale
MRS	-	modified Rankin Scale
STAT	-	Stroke Treatment with Ancrod Trial
ESTAT	-	European Stroke Treatment with Ancrod Trial
NINDS	-	National Institute of Neurological Disorders and stroke
LVD	-	Large vessel disease
SVD	–	small vessel disease

PROFORMA

NAME: IP NO: SERIAL NO:

AGE:

SEX:

OCCUPATION:

ADDRESS:

DATE AND TIME OF STROKE:

DATE OF ADMISSION:

STROKE RISK FACTORS

SHT Y/N

DM Y/N

SMOKING Y/N

ALCOHOLISM Y/N

HIGH CHOLESSTEROL Y/N

IHD Y/N

RHD Y/N

AF Y/N

PAST HISTORY OF STROKE : Y/N

CLINICAL EXAMINATION:

PULSE RATE: BP:

CVS:

RS:

ABDOMEN:

CNS:

ACUTE STROKE SYMPTOMS AND SIGNS

SYMPTOMS

HEADACHE

GIDDINESS

VOMITING

GAIT DISTURBANCE

CONVULSIONS

SPEECH DEFICIT

-

SIGNS

SPEECH DEFICIT

HEMIANOPIA

DIPLOPIA

MOTOR SYSTEM

PARESIS AT ANY SITE

PARESIS OF ARMS Y/N R/L/B

PARESI OF LEGS Y/N R/L/B

PARESIS OF FACE Y/N R/L/B

FIRST INVOLVED FACE / ARMS / LEGS

NO SUCH ORDER Y/N

SENSORY DEFICIT Y/N

CEREBELLAR SIGNS Y/N

MRS AFTER 8 WEEKS: 00/01/02/03/04/05/06

INVESTIGATIONS:

HB%:

TOTAL COUNT:

DIFFERENTIAL COUNT P- , L- , E- , M- , B-

ESR:

BLOOD UREA:

BLOOD SUGAR:

SERUM CREATININE:

SERUM ELECTROLYTES:

LIPID PROFILE:

PLASMA FIBRINOGEN:

ECG:

CT BRAIN AND FINDING:

HAEMORRHAGE : Y/N

INFARCT : Y/N

LOCATION : ACA/MCA/PCA

WATER SHED/GLOBAL/LACUNAR/OTHERS

THE NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

SCORE SHEET

ITEM	RESPONSE	SCORE
1a. Level of consciousness	0 = Alert 1 = Not alert 2 = Obtunded 3 = Unresponsive	
1b. Level of consciousness questions	0 = Answers both correctly 1 = Answers one correctly 2 =Answers neither correctly	
1c. Level of consciousness commands (2)	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task	
2. Gaze	0 = Normal 1 = Partial gaze palsy 2 = Total gaze palsy	
3. Visual fields	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia	

-

4. Facial palsy

0 = Normal

1 = Minor paralysis

2 = Partial paralysis

3 = Complete paralysis

5. Motor arm

a. Left

b. Right

0 = No drift

1 = Drift before 5 s

2 = Falls before 10 s

3 = No effort against gravity

4 = No movement R L

6. Motor leg

a. Left

b. Right

0 = No drift

1 = Drift before 5 s

2 = Falls before 5 s

3 = No effort against gravity

4 = No movement

R L

7. Ataxia

0 = Absent

1 = One limb

2 = Two limbs

8. Sensory

0 = Normal

1 = Mild loss

2 = Severe loss

9. Language

0 = Normal

1 = Mild aphasia

2 = Severe aphasia

3 = Mute or global aphasia

10. Dysarthria

0 = Normal

1 = Mild

2 = Severe

11. Extinction / inattention

0 = Normal

1 = Mild

2 = Severe

DATE OF ADMISSION NIHSS SCORE

MODIFIED RANKIN SCALE (MRS)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): ___

S.No.	Name	Age	Sex	**Smoke**	alcoholic	**Diabetic**	**HT**	Cholesterol	BMI	**NHSS**	**MRS**	**fibrinogen**	**symptom**	**Sign**	**CT**	**MRI**	**Syndrome**	**history**
1	Murugesan	40	male	Smoker	alcoholic	no DM	no HT	127	28.1	12	1	465	GD,dysphasia, FD R	FP,SP,HP R	LT MCA I		PACS	
2	Palanisamy	71	male	Smoker	alcoholic	no DM	HT	140	23.3	28	4	425	ALOC,APHAS, GD,VD	HP,FP,SP,ALOC	MAS I L m+a		TACS	TIA , CAD
3	Papammal	62	female	No	no	Diabetic	HT	245	23.3	9	1	360	GD,dysphasia, FD	FP,SP,HP R	MCAI L		PACS	
4	Chandrasekar	55	male	Smoker	no	no DM	HT	221	28.8	24	4	500	GD	HP R	N	LAC INF L	LACS	TIA
5	Subbiah	65	male	No	no	no DM	HT	130	24.1	4	0	380	GD, dysphasia,FD	FP,SP,HP L	MCAI R		PACS	
6	Nallathal	47	female	No	no	Diabetic	HT	230	24.5	10	1	410	GD, dysphasia,FD	FP,SP,HP R	MCAI L		PACS	
7	Ponnusamy	55	male	Smoker	no	Diabetic	no HT	220	29.2	5	1	315	GD	HP R	N	LAC INF L	LACS	
8	Karuppaiah	45	male	Smoker	alcoholic	no DM	no HT	151	33.5	25	3	680	ALOC,APHAS, GD,VD	ALOC,HP,SP,FP	MAS I R m+a		TACS	CAD
9	Gajalaxmi	41	female	No	no	Diabetic	no HT	188	21.8	12	2	265	vom,gid, incoord	nyst,CS	PCA L		PCS	
10	Anguselvan	52	male	Smoker	no	Diabetic	no HT	162	23.1	14	2	475	vom,gid,incoord	nyst,CS	PCAI R		PCS	
11	Chellam	63	female	No	no	Diabetic	HT	212	28.9	12	2	280	GD, dysphasia,FD	FP,SP,HP R	MCAI L		PACS	CAD
12	Syed Kadher	52	male	No	no	no DM	HT	242	31.1	10	2	485	GD,FD	HP,FP R		LAC INF L	LACS	
13	Muthammal	66	female	No	no	Diabetic	no HT	266	28.4	16	1	440	GD, dysphasia,FD	FP,SP,HP R	MCAI L		PACS	
14	Sundaram	46	male	Smoker	no	no DM	no HT	161	22.4	4	1	245	GD,	HP,FP L		LAC INF R	LACS	
15	Annamalai	44	male	Smoker	alcoholic	no DM	HT	186	32.1	24	4	510	ALOC, APHAS,GD,VD	ALOC,HP,SP,FP	MAS I Rm+a		TACS	TIA , CAD
16	Raju	65	male	Smoker	no	no DM	HT	220	31.8	23	4	520	GD,dysphasia ,FD	FP,SP,HP R	MCAI L		PACS	
17	Pandi	67	male	Smoker	alcoholic	Diabetic	HT	156	27.1	8	2	290	GD,FD	HP,FP L	N	LAC INF R	LACS	
18	Velmurugan	59	male	Smoker	alcoholic	no DM	HT	214	22.4	24	2	515	vom,gid,incoord	nyst,CS	PCAI R		PCS	TIA
19	Thoppan	75	male	Smoker	alcoholic	no DM	no HT	168	29.2	21	3	520	GD, dysphasia,FD	FP,SP,HP L	MCAI R		PACS	CAD
20	Maruthamal	53	female	No	no	Diabetic	HT	160	24.1	16	1	420	GD	HP L		LAC INF R	LACS	
21	Kasinathan	54	male	No	no	no DM	no HT	110	23.2	4	0	240	GD	HP R	N	LAC INF L	LACS	
22	Solaiyan	38	male	Smoker	alcoholic	Diabetic	HT	158	28.8	23	4	540	GD, dysphasia, FD	FP,SP,HP L	MCAI R		PACS	CAD
23	Mohdpitchai	62	male	Smoker	alcoholic	Diabetic	HT	220	29.7	12	3	420	GD,dysphasia,FD	FP,SP,HP L	MCAI R		PACS	
24	Veeranan	64	male	Smoker	no	no DM	no HT	116	21	5	1	250	GD	HP L		LAC INF R	PCS	
25	Janaki	35	female	No	no	no DM	HT	175	25.4	8	3	275	GD,FD	HP,FD R		LAC INF L	LACS	
26	Jeyakumar	45	male	Smoker	alcoholic	no DM	no HT	190	28.4	10	3	495	vom,gid,incoord	nyst,CS	PCAI R		PCS	CAD
27	Samy	54	male	Smoker	no	no DM	no HT	175	21.5	4	1	240	GD,Dysphasia,FD	FP,SP,HP R	MCAI L		PACS	
28	Panchavarnam	56	female	No	no	Diabetic	no HT	185	24.1	12	3	345	GD,dysphasia,FD	FP,SP,HP R	MCAI L		PACS	
29	Palanisamy	63	male	No	no	Diabetic	HT	220	24.6	6	2	295	vom,gid,incoord	nyst,CS	PCAI L		PCS	CAD
30	Chellaiya	30	male	Smoker	no	Diabetic	HT	215	29.1	16	3	365	GD,dysphasia,FD	FP,SP,HP R	MCAI L		PACS	
31	Kumaralaxmi	65	female	No	no	Diabetic	HT	246	28.5	28	5	620	ALOC,APHAS,GD,VD	ALOC,HP,SP,FP	MAS I Rm+a		TACS	TIA
32	Kandan	49	male	Smoker	alcoholic	no DM	no HT	195	24.6	16	3	375	GD,dysphasia,FD	FP,SP,HP L	MCAI R		PACS	TIA , CAD
33	Samiappan	52	male	Smoker	alcoholic	no DM	no HT	235	27.5	4	0	350	GD	HP R	N	LAC INF L	LACS	
34	Kadhar Ali	52	male	Smoker	no	no DM	HT	260	24.1	28	4	570	vom,gid,incoord	nyst,CS	PCAI R		PCS	CAD
35	Vellaiammal	60	female	No	no	Diabetic	no HT	185	23.1	5	1	320	vom,gid,incoord	nyst,CS	PCAI L		PCS	
36	Ulaganathan	58	male	Smoker	no	no DM	no HT	130	32.1	28	1	590	ALOC,APHAS,GD,VD	ALOC,HP,SP,FP	MAS I L		TACS	
37	Mahalingam	48	male	No	no	Diabetic	no HT	110	24.1	10	1	355	GD	HP L	N	LAC INF R	LACS	CAD
38	Ravichandiran	45	male	No	no	no DM	no HT	146	22	12	2	535	GD,Dysphasia FD	FP,SP,HP R	MCAI L		PACS	
39	Raman	71	male	Smoker	alcoholic	Diabetic	no HT	138	24.01	16	3	400	GD,FD	HP,FP L		LAC INF R	LACS	CAD
40	Duraisamy Kasi	62	male	Smoker	alcoholic	no DM	no HT	215	26.7	18	2	325	GD,dysphasia,FD	FP,SP,HP R	MCAI L		PACS	
41	Kani	52	male	Smoker	no	no DM	HT	290	31	27	4	575	GD, Dysphasia, FD	FP,SP,HP L	MCAI R		PACS	
42	Vijayakumar	60	male	Smoker	no	no DM	no HT	240	27.4	25	4	315	ALOC,APHAS,GD,VD	ALOC,HP,SP,FP	MAS I L		TACS	
43	Ayyanan	62	male	No	no	Diabetic	no HT	226	26	18	1	315	GD,dysphasia,FD	FP,SP,HP L	MCAI R		PACS	
44	Alagar	58	male	Smoker	alcoholic	no DM	no HT	146	23.1	3	0	295	vom,gid, incoord	nyst,CS	PCAI R		PCS	CAD
45	Pitchai	45	male	No	no	Diabetic	no HT	225	23	4	0	340	vom,gid, incoord	nyst,CS	P CAI L		PCS	
46	Ilangovan	47	male	No	no	Diabetic	HT	200	24	15	3	360	GD,FD	HP,FP R		LAC INF L	LACS	
47	Rakkayee	65	female	No	no	Diabetic	no HT	262	31.2	29	5	590	ALOC,APHAS, GD,VD	ALOC,HP,SP,FP	MAS I L		TACS	TIA , CAD
48	Thangapappan	45	male	Smoker	alcoholic	no DM	no HT	180	23.2	6	1	185	GD,FD	HP,FP L		LAC INF R	LACS	
49	Samayee	55	female	No	no	no DM	no HT	175	21.6	16	4	285	GD	HP R		LAC INF L	LACS	
50	Nagar	50	male	No	no	Diabetic	HT	218	24.1	14	3	310	GD,dysphasia, FD	FP,SP,HP L	MCAI R		PACS	TIA

CONTROL										
S,No.	**Name**	**Age**	**Sex**	**smoker**	**Drinker**	**DM**	**HT**	**Choles**	**BMI**	**fibrinogen**
1	ramasamy	57	male	smoker	alcoholic	Diabetic	no HT	192	22.6	370
2	sivam	61	male	smoker	no	no DM	no HT	176	19.1	165
3	samivelu	63	male	no	no	Diabetic	HT	190	24.1	280
4	veerammal	67	female	no	no	no DM	no HT	172	18.9	160
5	ponnusamy	78	male	no	no	Diabetic	no HT	152	23.2	295
6	kuppusamy	64	male	no	no	no DM	HT	132	31.4	245
7	samy	66	male	no	no	Diabetic	no HT	148	32.4	315
8	nathan	63	male	no	alcoholic	no DM	no HT	98	19.1	235
9	mohammed	48	male	no	no	no DM	no HT	115	21.2	160
10	Raja	56	male	no	no	Diabetic	no HT	140	21.6	280
11	arumugam	47	male	no	no	no DM	HT	200	22	216
12	rakammal	59	female	no	no	no DM	HT	225	22.4	225
13	murugan	57	male	smoker	alcoholic	Diabetic	HT	265	26.8	395
14	kanagammal	58	female	no	no	no DM	no HT	170	19.1	155
15	samiyandi	49	male	smoker	alcoholic	Diabetic	no HT	115	19.2	170
16	pandeeswari	48	female	no	no	no DM	no HT	158	18.9	225
17	revathy	36	female	no	no	no DM	no HT	118	22	170
18	baskaran	58	male	no	no	Diabetic	no HT	135	22.6	265
19	ramayee	51	female	no	no	no DM	HT	190	18.1	200
20	laxmiammal	62	female	no	no	no DM	no HT	115	22.1	235
21	muniasamy	50	male	smoker	alcoholic	Diabetic	no HT	236	20.4	360
22	pandiyan	44	male	no	no	no DM	HT	140	24.1	160
23	kaliammal	64	female	smoker	no	no DM	no HT	172	21.6	175
24	rajamani	63	male	smoker	alcoholic	no DM	no HT	126	22.3	275
25	abdul kadar	54	male	smoker	alcoholic	no DM	no HT	95	20.1	205
26	saravanan	57	male	smoker	alcoholic	no DM	no HT	140	19.4	260

CONTROL										
S,No.	**Name**	**Age**	**Sex**	**smoker**	**Drinker**	**DM**	**HT**	**Choles**	**BMI**	**fibrinogen**
27	rajamanikam	52	male	smoker	alcoholic	no DM	HT	172	22.4	270
28	rasiammal	64	female	no	no	Diabetic	HT	190	23.1	240
29	kamarajan	72	male	smoker	alcoholic	Diabetic	no HT	160	27.2	375
30	devaraj	74	male	no	no	Diabetic	no HT	170	32.4	320
31	gurusamy	62	male	smoker	no	no DM	no HT	95	19.1	245
32	sivaraman	63	male	smoker	alcoholic	no DM	no HT	166	21.2	260
33	kumaran	73	male	no	no	Diabetic	no HT	170	29.4	375
34	petchimuthu	62	male	smoker	alcoholic	Diabetic	HT	242	29	410
35	kannabiran	56	male	no	no	no DM	no HT	116	21.2	330
36	kalyanaraman	54	male	no	no	Diabetic	no HT	192	22.6	315
37	sekaran	55	male	no	no	Diabetic	no HT	172	23.2	245
38	muthukumaran	49	male	no	no	no DM	no HT	116	19.1	185
39	kumaraguru	48	male	smoker	alcoholic	no DM	no HT	155	22.1	215
40	sudar	66	female	no	no	no DM	no HT	140	24.7	165
41	sadaiyan	38	male	smoker	alcoholic	no DM	no HT	90	24.6	220
42	muniyandi	62	male	no	no	Diabetic	HT	192	26.5	350
43	thambiran	52	male	smoker	alcoholic	no DM	HT	190	26.5	345
44	kalairajan	39	male	smoker	alcoholic	no DM	no HT	130	24.3	160
45	rajendiran	34	male	smoker	alcoholic	no DM	no HT	135	21.2	230
46	seeni	48	male	no	no	Diabetic	HT	190	26.1	230
47	raman	66	male	smoker	alcoholic	Diabetic	HT	266	31.2	425
48	pachammal	44	female	no	no	Diabetic	HT	220	23.4	240
49	palaniappan	65	male	smoker	alcoholic	Diabetic	HT	250	29.2	325
50	chinnasamy	56	male	no	no	Diabetic	HT	220	23.4	315

MASTER CHART ABBREVIATIONS

GD	-	Gait Disturbance
FD	-	Facial deviation
APHAS	-	Aphasia
ALOL	-	Altered level of consciousness
GID	-	Giddiness
Vom	–	Vomiting
Incord	-	Incoordination
FP	-	Facial Palsy
SP	-	Speech disorder
HP	-	Hemiplegia
Nyst	-	Nystagmus
CS	-	Cerebellar Signs
R	-	Right
L	-	Left
N	-	Normal
LTMCA	-	Left middle cerebral artery
I	-	Infarction
PCAI	-	Posterior cerebral artery infarction
m + a	-	Middle cerebral artery & Anterior cerebral artery
LACI	-	LACUNAR Infarction
PCS	-	Posterior circulation syndrome
TACS	-	Total anterior circulation syndrome
PACS	-	Partial anterior circulation syndrome
LACS	-	LACUNAR Syndrome

Depart of Medicine

Ref. No. 5336 /E4/3/2012 Govt. Rajaji Hospital,
Madurai.20. Dated: .08.2012

Institutional Review Board / Independent Ethics Committee.
Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
Dean, Madurai Medical College & 2521021 (Secy)
Govt Rajaji Hospital, Madurai 625020.
Convenor
grhethicssecy @gmail.com.

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 28.06.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have been attended the meeting.

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1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G) 9894053516	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D, 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 2, Deputy collectors colony 4th street KK Nagar, Madurai-20.	Member
10.Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following Projects were approved by the committee

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Dr. Nachiappan.	M.D Gen med	Plasma fibrinogen as a prognostic indicator in cerebrovascular accidents.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.
She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8.She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

17.8.12

DEAN I/C.

48/58

To
All the above members and Head of the Departments concerned.
All the Applicants.

A STUDY ON SIGNIFICANCE OF FIBRINOGEN AS A RISKFACTOR FOR ISCHEMIC STROKE AND ITS CORRELATION WITH SEVERITY AND FUNCTIONAL OUTCOME OF ISCHEMIC STROKE

Dissertation submitted

in partial fulfillment for the Degree of

DOCTOR OF MEDICINE

BRANCH I - M.D., (General Medicine)

APRIL 2013

DEPARTMENT OF MEDICINE

MADURAI MEDICAL COLLEGE

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

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Assignment title	Medical
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A STUDY ON SIGNIFICANCE OF FIBRINOGEN AS A RISKFACTOR FOR ISCHEMIC STROKE AND ITS CORRELATION WITH SEVERITY AND FUNCTIONAL OUTCOME OF ISCHEMIC STROKE Dissertation submitted in partial fulfillment for the Degree of DOCTOR OF MEDICINE BRANCH I - M.D., (General Medicine) APRIL 2013 DEPARTMENT OF MEDICINE MADURAI MEDICAL COLLEGE THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY CHENNAI – TAMILNADU CERTIFICATE This is to certify that this dissertation entitled “A STUDY ON SIGNIFICANCE OF FIBRINOGEN AS A RISK FACTOR FOR ISCHEMIC STROKE AND ITS CORRELATION WITH SEVERITY AND FUNCTIONAL OUTCOME OF ISCHEMIC STROKE” ” submitted by Dr.K.NACHIAPPAN to The Tamil Nadu Dr.M.G.R. Medical University, Chennai is in...